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(54) Title: COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

(57) Abstract

Compounds and methods for treating lung cancer are provided. The inventive compounds include polypeptides containing at least a portion of a lung tumor protein. Vaccines and pharmaceutical compositions for immunotherapy of lung cancer comprising such polypeptides, or polynucleotides encoding such polypeptides, are also provided, together with polynucleotides for preparing the inventive polypeptides.

COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

TECHNICAL FIELD

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The present invention relates generally to compositions and methods for the treatment of lung cancer. The invention is more specifically related to nucleotide sequences that are preferentially expressed in lung tumor tissue, together with polypeptides encoded by such nucleotide sequences. The inventive nucleotide sequences and polypeptides may be used in vaccines and pharmaceutical compositions for the treatment of lung cancer.

BACKGROUND OF THE INVENTION

Lung cancer is the primary cause of cancer death among both men and women in the U.S., with an estimated 172,000 new cases being reported in 1994. The five-year survival rate among all lung cancer patients, regardless of the stage of disease at diagnosis, is only 13%. This contrasts with a five-year survival rate of 46% among cases detected while the disease is still localized. However, only 16% of lung cancers are discovered before the disease has spread.

Early detection is difficult since clinical symptoms are often not seen until the disease has reached an advanced stage. Currently, diagnosis is aided by the use of chest x-rays, analysis of the type of cells contained in sputum and fiberoptic examination of the bronchial passages. Treatment regimens are determined by the type and stage of the cancer, and include surgery, radiation therapy and/or chemotherapy. In spite of considerable research into therapies for the disease, lung cancer remains difficult to treat.

Accordingly, there remains a need in the art for improved vaccines, treatment methods and diagnostic techniques for lung cancer.

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compounds and methods for the therapy of lung cancer. In a first aspect, isolated polynucleotides encoding lung tumor polypeptides are provided, such polynucleotides comprising a nucleotide sequence selected

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herein; and (b) detecting in the sample a protein or polypeptide that binds to the binding agent. In preferred embodiments, the binding agent is an antibody, most preferably a monoclonal antibody.

In related aspects, methods are provided for monitoring the progression of lung cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to one of the polypeptides disclosed herein; (b) determining in the sample an amount of a protein or polypeptide that binds to the binding agent; (c) repeating steps (a) and (b); and comparing the amounts of polypeptide detected in steps (b) and (c).

Within related aspects, the present invention provides antibodies, preferably monoclonal antibodies, that bind to the inventive polypeptides, as well as diagnostic kits comprising such antibodies, and methods of using such antibodies to inhibit the development of lung cancer.

The present invention further provides methods for detecting lung cancer comprising: (a) obtaining a biological sample from a patient; (b) contacting the sample with a first and a second oligonucleotide primer in a polymerase chain reaction, at least one of the oligonucleotide primers being specific for a polynucleotide that encodes one of the polypeptides disclosed herein; and (c) detecting in the sample a DNA sequence that amplifies in the presence of the first and second oligonucleotide primers. In a preferred embodiment, at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181.

In a further aspect, the present invention provides a method for detecting lung cancer in a patient comprising: (a) obtaining a biological sample from the patient; (b) contacting the sample with an oligonucleotide probe specific for a polynucleotide that encodes one of the polypeptides disclosed herein; and (c) detecting in the sample a DNA sequence that hybridizes to the oligonucleotide probe. Preferably, the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181. In related a spects, diagnostic kits comprising the above oligonucleotide probes or primers are provided.

SEQ ID NO: 14 is the determined cDNA sequence for L355C1.cons SEQ ID NO: 15 is the determined cDNA sequence for L366C1.cons SEQ ID NO: 16 is the determined cDNA sequence for L163C1a SEQ ID NO: 17 is the determined cDNA sequence for LT86-1 SEQ ID NO: 18 is the determined cDNA sequence for LT86-2 SEQ ID NO: 19 is the determined cDNA sequence for LT86-3 SEQ ID NO: 20 is the determined cDNA sequence for LT86-4 SEQ ID NO: 21 is the determined cDNA sequence for LT86-5' SEQ ID NO: 22 is the determined cDNA sequence for LT86-6 10 SEQ ID NO: 23 is the determined cDNA sequence for LT86-7 SEQ ID NO: 24 is the determined cDNA sequence for LT86-8 SEQ ID NO: 25 is the determined cDNA sequence for LT86-9 SEQ ID NO: 26 is the determined cDNA sequence for LT86-10 SEQ ID NO: 27 is the determined cDNA sequence for LT86-11 SEQ ID NO: 28 is the determined cDNA sequence for LT86-12 SEQ ID NO: 29 is the determined cDNA sequence for LT86-13 SEQ ID NO: 30 is the determined cDNA sequence for LT86-14 SEQ ID NO: 31 is the determined cDNA sequence for LT86-15 SEQ ID NO: 32 is the predicted amino acid sequence for LT86-1 SEQ ID NO: 33 is the predicted amino acid sequence for LT86-2 SEQ ID NO: 34 is the predicted amino acid sequence for LT86-3 SEQ ID NO: 35 is the predicted amino acid sequence for LT86-4 SEQ ID NO: 36 is the predicted amino acid sequence for LT86-5 SEQ ID NO: 37 is the predicted amino acid sequence for LT86-6 SEQ ID NO: 38 is the predicted amino acid sequence for LT86-7 SEQ ID NO: 39 is the predicted amino acid sequence for LT86-8 SEQ ID NO: 40 is the predicted amino acid sequence for LT86-9 SEQ ID NO: 41 is the predicted amino acid sequence for LT86-10 SEQ ID NO: 42 is the predicted amino acid sequence for LT86-11 SEQ ID NO: 43 is the predicted amino acid sequence for LT86-12

SEQ ID NO: 74 is the predicted amino acid sequence for LT86-21 SEQ ID NO: 75 is the predicted amino acid sequence for LT86-22 SEQ ID NO: 76 is the predicted amino acid sequence for LT86-26 SEQ ID NO: 77 is the predicted amino acid sequence for LT86-27 SEQ ID NO: 78 is the determined extended cDNA sequence for L86S-12 SEQ ID NO: 79 is the determined extended cDNA sequence for L86S-36 SEQ ID NO: 80 is the determined extended cDNA sequence for L86S-46 SEQ ID NO: 81 is the predicted extended amino acid sequence for L86S-12 SEQ ID NO: 82 is the predicted extended amino acid sequence for L86S-36 SEQ ID NO: 83 is the predicted extended amino acid sequence for L86S-46 SEQ ID NO: 84 is the determined 5'cDNA sequence for L86S-6 SEQ ID NO: 85 is the determined 5'cDNA sequence for L86S-11 SEQ ID NO: 86 is the determined 5'cDNA sequence for L86S-14 SEQ ID NO: 87 is the determined 5'cDNA sequence for L86S-29 SEQ ID NO: 88 is the determined 5'cDNA sequence for L86S-34 SEQ ID NO: 89 is the determined 5'cDNA sequence for L86S-39 SEQ ID NO: 90 is the determined 5'cDNA sequence for L86S-47 SEQ ID NO: 91 is the determined 5'cDNA sequence for L86S-49 SEQ ID NO: 92 is the determined 5'cDNA sequence for L86S-51 SEQ ID NO: 93 is the predicted amino acid sequence for L86S-6 SEQ ID NO: 94 is the predicted amino acid sequence for L86S-11 SEQ ID NO: 95 is the predicted amino acid sequence for L86S-14 SEQ ID NO: 96 is the predicted amino acid sequence for L86S-29 SEQ ID NO: 97 is the predicted amino acid sequence for L86S-34 SEQ ID NO: 98 is the predicted amino acid sequence for L86S-39 SEQ ID NO: 99 is the predicted amino acid sequence for L86S-47 SEQ ID NO: 100 is the predicted amino acid sequence for L86S-49 SEQ ID NO: 101 is the predicted amino acid sequence for L86S-51 SEQ ID NO: 102 is the determined DNA sequence for SLT-T1

SEQ ID NO: 103 is the determined 5' cDNA sequence for SLT-T2

SEQ ID NO: 134 is the determined cDNA sequence for PSLT-69 SEQ ID NO: 135 is the determined cDNA sequence for PSLT-71 SEQ ID NO: 136 is the determined cDNA sequence for PSLT-73 SEQ ID NO: 137 is the determined cDNA sequence for PSLT-79 SEQ ID NO: 138 is the determined cDNA sequence for PSLT-03 SEQ ID NO: 139 is the determined cDNA sequence for PSLT-09 SEQ ID NO: 140 is the determined cDNA sequence for PSLT-011 SEQ ID NO: 141 is the determined cDNA sequence for PSLT-041 SEQ ID NO: 142 is the determined cDNA sequence for PSLT-62 SEQ ID NO: 143 is the determined cDNA sequence for PSLT-6 SEQ ID NO: 144 is the determined cDNA sequence for PSLT-37 SEQ ID NO: 145 is the determined cDNA sequence for PSLT-74 SEQ ID NO: 146 is the determined cDNA sequence for PSLT-010 SEQ ID NO: 147 is the determined cDNA sequence for PSLT-012 SEQ ID NO: 148 is the determined cDNA sequence for PSLT-037 SEQ ID NO: 149 is the determined 5' cDNA sequence for SAL-3 SEQ ID NO: 150 is the determined 5' cDNA sequence for SAL-24 SEQ ID NO: 151 is the determined 5' cDNA sequence for SAL-25 SEQ ID NO: 152 is the determined 5' cDNA sequence for SAL-33 SEQ ID NO: 153 is the determined 5' cDNA sequence for SAL-50 SEQ ID NO: 154 is the determined 5' cDNA sequence for SAL-57 SEQ ID NO: 155 is the determined 5° cDNA sequence for SAL-66 SEQ ID NO: 156 is the determined 5' cDNA sequence for SAL-82 SEQ ID NO: 157 is the determined 5' cDNA sequence for SAL-99 SEQ ID NO: 158 is the determined 5' cDNA sequence for SAL-104 SEQ ID NO: 159 is the determined 5' cDNA sequence for SAL-109 SEQ ID NO: 160 is the determined 5' cDNA sequence for SAL-5 SEQ ID NO: 161 is the determined 5' cDNA sequence for SAL-8 SEQ ID NO: 162 is the determined 5' cDNA sequence for SAL-12 SEQ ID NO: 163 is the determined 5' cDNA sequence for SAL-14

SEQ ID NO: 194 is the predicted amino acid sequence for SAL-5 SEQ ID NO: 195 is the predicted amino acid sequence for SAL-8 SEQ ID NO: 196 is the predicted amino acid sequence for SAL-12 SEQ ID NO: 197 is the predicted amino acid sequence for SAL-14 SEQ ID NO: 198 is the predicted amino acid sequence for SAL-16 SEQ ID NO: 199 is the predicted amino acid sequence for SAL-23 SEQ ID NO: 200 is the predicted amino acid sequence for SAL-26 SEQ ID NO: 201 is the predicted amino acid sequence for SAL-29 SEQ ID NO: 202 is the predicted amino acid sequence for SAL-32 SEQ ID NO: 203 is the predicted amino acid sequence for SAL-39 SEQ ID NO: 204 is the predicted amino acid sequence for SAL-42 SEQ ID NO: 205 is the predicted amino acid sequence for SAL-43 SEQ ID NO: 206 is the predicted amino acid sequence for SAL-44 SEQ ID NO: 207 is the predicted amino acid sequence for SAL-48 SEQ ID NO: 208 is the predicted amino acid sequence for SAL-68 SEQ ID NO: 209 is the predicted amino acid sequence for SAL-72 SEQ ID NO: 210 is the predicted amino acid sequence for SAL-77 SEQ ID NO: 211 is the predicted amino acid sequence for SAL-86 SEQ ID NO: 212 is the predicted amino acid sequence for SAL-88 SEQ ID NO: 213 is the predicted amino acid sequence for SAL-93 SEQ ID NO: 214 is the predicted amino acid sequence for SAL-100 SEQ ID NO: 215 is the predicted amino acid sequence for SAL-105 SEQ ID NO: 216 is a second predicted amino acid sequence for SAL-50

25 DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy of lung cancer. The compositions described herein include polypeptides, fusion proteins and polynucleotides. Also included within the present invention are molecules (such as an antibody or fragment thereof) that bind to the inventive polypeptides. Such molecules are referred to herein as "binding agents."

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of the proteins described herein may be identified in antibody binding assays. Such assays may generally be performed using any of a variety of means known to those of ordinary skill in the art, as described, for example, in Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1988. For example, a polypeptide may be immobilized on a solid support (as described below) and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ¹²⁵I-labeled Protein A. Alternatively, a polypeptide may be used to generate monoclonal and polyclonal antibodies for use in detection of the polypeptide in blood or other fluids of lung cancer patients. Methods for preparing and identifying immunogenic portions of antigens of known sequence are well known in the art and include those summarized in Paul, Fundamental Immunology, 3rd ed., Raven Press, 1993, pp. 243-247.

The term "polynucleotide(s)," as used herein, means a single or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases and includes DNA and corresponding RNA molecules, including HnRNA and mRNA molecules, both sense and anti-sense strands, and comprehends cDNA, genomic DNA and recombinant DNA, as well as wholly or partially synthesized polynucleotides. An HnRNA molecule contains introns and corresponds to a DNA molecule in a generally one-to-one manner. An mRNA molecule corresponds to an HnRNA and DNA molecule from which the introns have been excised. A polynucleotide may consist of an entire gene, or any portion thereof. Operable anti-sense polynucleotides may comprise a fragment of the corresponding polynucleotide, and the definition of "polynucleotide" therefore includes all such operable anti-sense fragments.

The compositions and methods of the present invention also encompass variants of the above polypeptides and polynucleotides.

A polypeptide "variant," as used herein, is a polypeptide that differs from the recited polypeptide only in conservative substitutions and/or modifications, such that the antigenic properties of the polypeptide are retained. In a preferred embodiment, variant polypeptides differ from an identified sequence by substitution, deletion or addition of five amino acids or fewer. Such variants may generally be identified by modifying one of the above polypeptide sequences, and evaluating the antigenic properties of the modified polypeptide using, for example, the representative procedures described herein. Polypeptide

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SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5X SSC, overnight or, in the event of cross-species homology, at 45°C with 0.5X SSC; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. Such hybridizing DNA sequences are also within the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode an immunogenic polypeptide that is encoded by a hybridizing DNA sequence.

Two nucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acid residues in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins - Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Resarch Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 Methods in Enzymology vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) Fast and sensitive multiple sequence alignments on a microcomputer CABIOS 5:151-153; Myers, E.W. and Muller W. (1988) Optimal alignments in linear space CABIOS 4:11-17; Robinson, E.D. (1971) Comb. Theor 11:105; Santou, N. Nes, M. (1987) The neighbor joining method. A new method for reconstructing phylogenetic trees Mol. Biol. Evol. 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) Numerical Taxonomy - the Principles and Practice of Numerical Taxonomy, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) Rapid similarity searches of nucleic acid and protein data banks Proc. Natl. Acad., Sci. USA 80:726-730.

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libraries prepared from SCID mice with mouse anti-tumor sera, as described below in Example 4. Examples of cDNA sequences that may be isolated using this technique are provided in SEQ ID NO: 149-181.

A gene encoding a polypeptide described herein (or a portion thereof) may, alternatively, be amplified from human genomic DNA, or from lung tumor cDNA, via polymerase chain reaction. For this approach, sequence-specific primers may be designed based on the nucleotide sequences provided herein and may be purchased or synthesized. An amplified portion of a specific nucleotide sequence may then be used to isolate the full length gene from a human genomic DNA library or from a lung tumor cDNA library, using well known techniques, such as those described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY (1989).

Once a DNA sequence encoding a polypeptide is obtained, the polypeptide may be produced recombinantly by inserting the DNA sequence into an expression vector and expressing the polypeptide in an appropriate host. Any of a variety of expression vectors known to those of ordinary skill in the art may be employed to express recombinant polypeptides of this invention. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a polynucleotide that encodes the recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line, such as COS or CHO cells. The DNA sequences expressed in this manner may encode naturally occurring polypeptides, portions of naturally occurring polypeptides, or other variants thereof. Supernatants from suitable host/vector systems which secrete the recombinant polypeptide may be first concentrated using a commercially available filter. The concentrate may then be applied to a suitable purification matrix, such as an affinity matrix or ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify the recombinant polypeptide.

Such techniques may also be used to prepare polypeptides comprising portions or variants of the native polypeptides. Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as

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extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., Gene 40:39-46, 1985; Murphy et al., Proc. Natl. Acad. Sci. USA 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may be from 1 to about 50 amino acids in length. Peptide sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons require to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91 (1997)).

Polypeptides that comprise an immunogenic portion of a lung tumor protein may generally be used for therapy of lung cancer, wherein the polypeptide stimulates the patient's own immune response to lung tumor cells. The present invention thus provides methods for using one or more of the compounds described herein (which may be polypeptides, polynucleotides or fusion proteins) for immunotherapy of lung cancer in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may be afflicted with disease, or may be free of detectable disease. Accordingly, the compounds disclosed herein may be used to treat lung cancer or to inhibit the development of lung cancer. In a preferred embodiment, the compounds are administered

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ordinary skill in the art. The DNA may also be "naked," as described, for example, in published PCT application WO 90/11092, and Ulmer et al., Science 259:1745-1749, 1993, reviewed by Cohen, Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

Routes and frequency of administration, as well as dosage, will vary from individual to individual and may parallel those currently being used in immunotherapy of other diseases. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Between 1 and 10 doses may be administered over a 3-24 week period. Preferably, 4 doses are administered, at an interval of 3 months, and booster administrations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of polypeptide or DNA that is effective to raise an immune response (cellular and/or humoral) against lung tumor cells in a treated patient. A suitable immune response is at least 10-50% above the basal (i.e., untreated) level. In general, the amount of polypeptide present in a dose (or produced in situ by the DNA in a dose) ranges from about 1 pg to about 100 mg per kg of host, typically from about 10 pg to about 1 mg, and preferably from about 100 pg to about 1 µg. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.01 mL to about 5 mL.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a lipid, a wax and/or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and/or magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactic glycolide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S.

30 Patent Nos. 4,897,268 and 5,075,109.

(Natural Killer cells, lymphokine-activated killer cells), B cells, or antigen presenting cells (such as dendritic cells and macrophages) expressing the disclosed antigens. The polypeptides disclosed herein may also be used to generate antibodies or anti-idiotypic antibodies (as in U.S. Patent No. 4,918,164), for passive immunotherapy.

The predominant method of procuring adequate numbers of T-cells for adoptive immunotherapy is to grow immune T-cells in vitro. Culture conditions for expanding single antigen-specific T-cells to several billion in number with retention of antigen recognition in vivo are well known in the art. These in vitro culture conditions typically utilize intermittent stimulation with antigen, often in the presence of cytokines, such as IL-2, and non-dividing feeder cells. As noted above, the immunoreactive polypeptides described herein may be used to rapidly expand antigen-specific T cell cultures in order to generate sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage or B-cells, may be pulsed with immunoreactive polypeptides or transfected with a polynucleotide sequence(s), using standard techniques well known in the art. For cultured T-cells to be effective in therapy, the cultured T-cells must be able to grow and distribute widely and to survive long term in vivo. Studies have demonstrated that cultured T-cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al. Ibid).

The polypeptides disclosed herein may also be employed to generate and/or isolate tumor-reactive T-cells, which can then be administered to the patient. In one

technique, antigen-specific T-cell lines may be generated by *in vivo* immunization with short peptides corresponding to immunogenic portions of the disclosed polypeptides. The resulting antigen specific CD8+ CTL clones may be isolated from the patient, expanded using standard

tissue culture techniques, and returned to the patient.

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Alternatively, peptides corresponding to immunogenic portions of the polypeptides may be employed to generate tumor reactive T cell subsets by selective in vitro stimulation and expansion of autologous T cells to provide antigen-specific T cells which may be subsequently transferred to the patient as described, for example, by Chang et al. (Crit. Rev. Oncol. Hematol., 22(3), 213, 1996).

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at least about 80%, and preferably at least about 90%) of the patients for which lung cancer would be indicated using the full length protein, and that indicate the absence of lung cancer in substantially all of those samples that would be negative when tested with full length protein. The representative assays described below, such as the two-antibody sandwich 5 assay, may generally be employed for evaluating the ability of a binding agent to detect metastatic human lung tumors.

The ability of a polypeptide prepared as described herein to generate antibodies capable of detecting primary or metastatic human lung tumors may generally be evaluated by raising one or more antibodies against the polypeptide (using, for example, a representative method described herein) and determining the ability of such antibodies to detect such tumors in patients. This determination may be made by assaying biological samples from patients with and without primary or metastatic lung cancer for the presence of a polypeptide that binds to the generated antibodies. Such test assays may be performed, for example, using a representative procedure described below. Polypeptides that generate 15 antibodies capable of detecting at least 20% of primary or metastatic lung tumors by such procedures are considered to be useful in assays for detecting primary or metastatic human lung tumors. Polypeptide specific antibodies may be used alone or in combination to improve sensitivity.

Polypeptides capable of detecting primary or metastatic human lung tumors 20 may be used as markers for diagnosing lung cancer or for monitoring disease progression in patients. In one embodiment, lung cancer in a patient may be diagnosed by evaluating a biological sample obtained from the patient for the level of one or more of the above polypeptides, relative to a predetermined cut-off value. As used herein, suitable "biological samples" include blood, sera, urine and/or lung secretions.

The level of one or more of the above polypeptides may be evaluated using any binding agent specific for the polypeptide(s). A "binding agent," in the context of this invention, is any agent (such as a compound or a cell) that binds to a polypeptide as described above. As used herein, "binding" refers to a noncovalent association between two separate molecules (each of which may be free (i.e., in solution) or present on the surface of a cell or a solid support), such that a "complex" is formed. Such a complex may be free or immobilized (either covalently or noncovalently) on a support material. The ability to bind may generally

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be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the antigen and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 µg, and preferably about 100 ng to about 1 µg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a second antibody (containing a reporter group) capable of binding to a different site on the polypeptide is added. The amount of second antibody that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20TM (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is

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that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without lung cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for lung cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for lung cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the antibody is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized antibody as the sample passes through the membrane. A second, labeled antibody then binds to the antibody-polypeptide complex as a solution containing the second antibody flows through the membrane. The detection of bound second antibody may then be performed as described above. In the strip test format, one end of the membrane to which antibody is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second antibody and to the area of immobilized antibody. Concentration of second antibody at the area of immobilized antibody indicates the presence of lung cancer. Typically, the concentration of second antibody at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of antibody immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody

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of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Monoclonal antibodies of the present invention may also be used as therapeutic reagents, to diminish or eliminate lung tumors. The antibodies may be used on their own (for instance, to inhibit metastases) or coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ⁹⁰Y, ¹²³I, ¹²⁵I, ¹³¹I, ¹²⁶Re, ¹²⁸Re, ²¹¹At, and ²¹²Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction

be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

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Diagnostic reagents of the present invention may also comprise DNA sequences encoding one or more of the above polypeptides, or one or more portions thereof. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify lung tumor-specific cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for a polynucleotide encoding a lung tumor protein of the present invention. The presence of the amplified cDNA is then detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes specific for a polynucleotide encoding a lung tumor protein of the present invention may be used in a hybridization assay to detect the presence of an inventive polypeptide in a biological sample.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

PREPARATION OF LUNG TUMOR-SPECIFIC cDNA SEQUENCES USING DIFFERENTIAL DISPLAY RT-PCR

This example illustrates the preparation of cDNA molecules encoding lung tumor-specific polypeptides using a differential display screen.

Tissue samples were prepared from breast tumor and normal tissue of a patient with lung cancer that was confirmed by pathology after removal of samples from the patient. Normal RNA and tumor RNA was extracted from the samples and mRNA was isolated and converted into cDNA using a (dT)₁₂AG (SEQ ID NO: 47) anchored 3' primer. Differential display PCR was then executed using a randomly chosen primer (SEQ ID NO: 48). Amplification conditions were standard buffer containing 1.5 mM MgCl₂, 20 pmol of primer, 500 pmol dNTP and 1 unit of Taq DNA polymerase (Perkin-Elmer, Branchburg, NJ). Forty cycles of amplification were performed using 94 °C denaturation for 30 seconds, 42 °C annealing for 1 minute and 72 °C extension for 30 seconds. Bands that were repeatedly observed to be specific to the RNA fingerprint pattern of the tumor were cut out of a silver stained gel, subcloned into the pGEM-T vector (Promega, Madison, WI) and sequenced. The isolated 3' sequences are provided in SEQ ID NO: 1-16.

Comparison of these sequences to those in the public databases using the BLASTN program, revealed no significant homologies to the sequences provided in SEQ ID NO: 1-11. To the best of the inventors' knowledge, none of the isolated DNA sequences have previously been shown to be expressed at a greater level in human lung tumor tissue than in normal lung tissue.

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aminopeptidase. Clone LT86-9 appears to contain two inserts, with the 5' sequence showing homology to the previously identified antisense sequence of interferon alpha-induced P27, and the 3' sequence being similar to LT86-6. Clone LT86-14 (SEQ ID NO: 30) was found to show some homology to the trithorax gene and has an "RGD" cell attachment sequence and a beta-Lactamase A site which functions in hydrolysis of penicillin. Clones LT86-1, LT86-2, LT86-4, LT86-5 and LT86-10 (SEQ ID NOS: 17, 18; 20, 21 and 26, respectively) were found to show homology to previously identified genes. A subsequently determined extended cDNA sequence for LT86-4 is provided in SEQ ID NO: 66, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 67.

Subsequent studies led to the isolation of five additional clones, referred to as LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27. The determined 5' cDNA sequences for LT86-20, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 68 and 70-72, respectively, with the determined 3' cDNA sequences for LT86-21 being provided in SEQ ID NO: 69. The corresponding predicted amino acid sequences for LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 73-77, respectively. LT86-22 and LT86-27 were found to be highly similar to each other. Comparison of these sequences to those in the gene bank as described above, revealed no significant homologies to LT86-22 and LT86-27. LT86-20, LT86-21 and LT86-26 were found to show homology to previously identified genes.

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predicted amino acid sequences are provided in SEQ ID NO: 93-101, respectively. L86S-30, L86S-39 and L86S-47 were found to be similar to each other. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to L86S-14. L86S-29 was found to show some homology to a previously identified EST. L86S-6, L86S-11, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 were found to show some homology to previously identified genes.

In further studies, a directional cDNA library was constructed using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was isolated from two primary squamous lung tumors and poly A+RNA was isolated using an oligo dT column. Antiserum was developed in normal mice using a pool of sera from three SCID mice implanted with human squamous lung carcinomas. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli* absorbed mouse anti-SCID tumor serum. Positive plaques were identified as described above. Phage was purified and phagemid excised for 180 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 23 of the isolated clones are provided in SEQ ID NO: 126-148. Comparison of these sequences with those in the public database as described above revealed no significant homologies to the sequences of SEQ ID NO: 139 and 143-148. The sequences of SEQ ID NO: 126-138 and 140-142 were found to show homology previously identified human polynucleotide sequences.

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tags (ESTs). The sequences of SEQ ID NO: 150, 155 and 159-181 were found to show homology to sequences previously identified in humans.

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Example 6

ISOLATION OF DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

DNA sequences encoding antigens potentially involved in squamous cell lung tumor formation were isolated as follows.

A lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a pool of two human squamous epithelial lung carcinomas and poly A+ RNA was isolated using oligo-dT cellulose (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined cDNA sequence for the clone SLT-T1 is provided in SEQ ID NO: 102, with the determined 5' cDNA sequences for the clones SLT-T2, SLT-T3, SLT-T5. SLT-T7, SLT-T9, SLT-T10, SLT-T11 and SLT-T12 being provided in SEQ ID NO: 103-110, respectively. The corresponding predicted amino acid sequence for SLT-T1, SLT-T2, 15 SLT-T3, SLT-T10 and SLT-T12 are provided in SEQ ID NO: 111-115, respectively. Comparison of the sequences for SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9 and SLT-T11 with those in the public databases as described above, revealed no significant homologies. The sequences for SLT-T10 and SLT-T12 were found to show some homology to sequences previously identified in humans.

20 The sequence of SLT-T1 was determined to show some homology to a PAC clone of unknown protein function. The cDNA sequence of SLT-T1 (SEQ ID NO: 102) was found to contain a mutator (MUTT) domain. Such domains are known to function in removal of damaged guanine from DNA that can cause A to G transversions (see, for example, el-Deiry, W.S., 1997 Curr. Opin. Oncol. 9:79-87; Okamoto, K. et al. 1996 Int. J. Cancer 65:437-41; Wu, C. et al. 1995 Biochem. Biophys. Res. Commun. 214:1239-45; Porter, D.W. et al. 1996 Chem. Res. Toxicol. 9:1375-81). SLT-T1 may thus be of use in the treatment, by gene therapy, of lung cancers caused by, or associated with, a disruption in DNA repair.

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Example 7 SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0:1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

- A vaccine comprising the polypeptide of claim 2 and an immune response enhancer.
- 5 10. The vaccine of claim 9 wherein the immune response enhancer is an adjuvant.
 - 11. A vaccine comprising the polynucleotide of claims 1 or 4 and an immune response enhancer.
 - 12. The vaccine of claim 11 wherein the immune response enhancer is an adjuvant.

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- 13. A pharmaceutical composition for the treatment of lung cancer comprising a polypeptide and a physiologically acceptable carrier, the polypeptide comprising an immunogenic portion of a lung protein or of a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of:
 - (a) sequences recited in SEQ ID NO: 12-18, 20, 21, 26, 49, 50, 52, 54, 64, 66, 68, 69, 71, 78, 84, 85, 88, 91, 92, 116-120, 126-138, 140-142, 150, 155 and 159-181;
 - (b) sequences complementary to the sequences of SEQ ID NO: 12-18, 20, 21, 26, 49, 50, 52, 54, 64, 66, 68, 69, 71, 78, 84, 85, 88, 91, 92, 116-120, 126-138, 140-142, 150, 155 and 159-181; and
 - (c) variants of the sequences of (a) and (b).

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- 14. A vaccine for the treatment of lung cancer comprising a polypeptide and an immune response enhancer, said polypeptide comprising an immunogenic portion of a lung protein or of a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of:
- (a) sequences recited in SEQ ID NO: 12-18, 20, 21, 26, 49, 50, 52, 54, 64, 66, 68, 69, 71, 78, 84, 85, 88, 91, 92, 116-120, 126-138, 140-142, 150, 155 and 159-181;

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- 21. A pharmaceutical composition comprising a fusion protein according to any one of claims 18-20 and a physiologically acceptable carrier.
- 5 22. A vaccine comprising a fusion protein according to any one of claims 18-20 and an immune response enhancer.
 - 23. The vaccine of claim 22 wherein the immune response enhancer is an adjuvant.
 - 24. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient an effective amount of the pharmaceutical composition of claim 21.
 - 25. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient an effective amount of the vaccine of claim 22.
 - 26. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient a polynucleotide under conditions such that the polynucleotide enters a cell of the patient and is expressed therein, the polynucleotide having a sequence selected from the group consisting of:
 - (a) a sequence provided in SEQ ID NO: 102;
 - (b) sequences complementary to a sequence of SEQ ID NO: 102; and
 - (c) variants of the sequence of SEQ ID NO: 102.
 - 27. A method for detecting lung cancer in a patient, comprising:
 - (a) contacting a biological sample obtained from the patient with a binding agent which is capable of binding to a polypeptide, the polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of sequences provided in SEQ ID NO: 1-31, 49-

- (a) sequences recited in SEQ ID NO: 1-11, 19, 22-25, 27-31, 51, 53, 55, 63, 70, 72, 79, 80, 86, 87, 89, 90, 102-107, 109, 139, 143-149, 151-154 and 156-158;
- (b) the complements of nucleotide sequences recited in SEQ ID NO: 1-11, 19, 22-25, 27-31, 51, 53, 55, 63, 70, 72, 79, 80, 86, 87, 89, 90, 102-107, 109, 139, 143-149, 151-154 and 156-158; and
- (c) variants of the sequences of (a) and (b).
- 32. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient a therapeutically effective amount of a monoclonal antibody according to claim 31.
 - 33. The method of claim 32 wherein the monoclonal antibody is conjugated to a therapeutic agent.
 - 34. A method for detecting lung cancer in a patient comprising:
 - (a) obtaining a biological sample from the patient;
- (b) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein at least one of the oligonucleotides is specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181, the complements of said sequences and variants thereof; and
- (c) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers, thereby detecting lung cancer.
- 35. The method of claim 34, wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181.

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provided in SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181, the complements of said sequences and variants thereof.

- 44. A method for detecting lung cancer in a patient, comprising:
- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with an oligonucleotide probe specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181, the complements of said nucleotide sequences and variants thereof; and
- (c) detecting in the sample a DNA sequence that hybridizes to the oligonucleotide probe, thereby detecting lung cancer in the patient.
- 45. The method of claim 44 wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide having a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181, the complements of said nucleotide sequences and variants thereof.
- 46. A diagnostic kit comprising an oligonucleotide probe specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181, the complements of said sequences and variants thereof.
- 47. The diagnostic kit of claim 46, wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide having a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 1-31, 49-55,

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pharmaceutically acceptable carrier.

- 55. A composition for the treatment of lung cancer in a patient, comprising T cells proliferated in the presence of a polynucleotide of claim 1, in combination with a pharmaceutically acceptable carrier.
 - 56. A method for treating lung cancer in a patient, comprising the steps of:
 - (a) incubating antigen presenting cells in the presence of at least one polypeptide of claim 2; and
 - (b) administering to the patient the incubated antigen presenting cells.
 - 57. A method for treating lung cancer in a patient, comprising the steps of:
 - (a) incubating antigen presenting cells in the presence of at least one polynucleotide of claim 1; and
 - (b) administering to the patient the incubated antigen presenting cells.
 - 58. The method of claims 54 or 55 wherein the antigen presenting cells are selected from the group consisting of dendritic cells and macrophage cells.
- 59. A composition for the treatment of lung cancer in a patient, comprising antigen presenting cells incubated in the presence of a polypeptide of claim 2, in combination with a pharmaceutically acceptable carrier.
- 60. A composition for the treatment of lung cancer in a patient, comprising antigen presenting cells incubated in the presence of a polynucleotide of claim 1, in combination with a pharmaceutically acceptable carrier.

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Lys Lys His Pro Asp Phe				Pro Tyr	
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.35 ·					راغا الشي الأرادة الما
Phe Phe Met Glu Lys Arg			Twe Len		
50/7	55	<u> </u>	60		74. A.
50xx		· .		- 1	
Ser Asn Leu Asp Leu Thr					
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Thr Gly Val Arg Ala Lys					•
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	TIE Wall		ser 11.b		van GIÀ
20		25	•	30	
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ser the cha wer wid wer	Gin II6	nea gra	CAP LTO	nen bro	wah aro

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Ası 65		Lys	s His	His	70		Lys	Glu	Met	Arg 75		Leu	. Met	Lys	s Val 80
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320

. 310

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His Leu Asn Gln Met Val Gly Ile Glu Tyr Ile Leu Leu His Ala Gln 65 70 75 80

Glu Pro Ile Leu Phe Ile Ile Arg Lys Gln Gln Arg Gln Ser Pro Ala 85 90 95

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Gln Ala Pro Asp Leu Gly Ser Val Ile Asn Ser Arg Val Leu Thr Ala 115 120 125

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Ile	Phe	Gln	Arg 180		Arg	Val	Asp	Ala 185	Leu	Leu	Leu	Asp	Leu 190	_	G1n	
Lys	Ile	Ser 195		Gln	Ile	Суз	Ala 200	Val	Asp	Gln	Thr	Lys 205	_	Glu	Ala	â
Glu	Pro 210		Pro	Glu	Thr	Val 215	Lys	Pro	Glu	Glu	Lys 220	Glu :	Thr	Thr	Lys	
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Arg	Leu	Gln					.,			٠.				: :		·
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	•	omo s	sapie	ens		·										: .
	0> 40 . A1a.		λen	Tle	Ara	Agn	Δen	T 0	_	G1v	Tla	Sar	Tra	V-1) Non	_
_									1.611	0.17		OCI	TT D	Val	Pap	•
.1			-	5				ren	Leu 10	·	. 1		•	15		
	Ser	Trp		5	Ile				10					15 Tyr	٠.	
Ser			Ile 20	5 Pro	Ile Pro	Leu	Asn	Ser 25	10 Gly	Ser	Val	Leu	Asp 30	15 Tyr	Phe	
Ser Ser	Glu	Arg 35	Ile 20 Ser	5 Pro Asn		Leu Phe	Asn Tyr 40	Ser 25 Asp	10 Gly Arg	Ser Thr	Val Cys	Leu Asn 45	Asp 30 Asn	15 Tyr Glu	Phe Val	
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Gly Pro Ser Gly Ala Ala Ala Lys Ile Pro Leu Glu Leu Thr Gln Ser

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Arg Ser Cys Gly Pro Lys Leu Thr Asn Ser Pro Ala Val Phe Val Met

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Leu	Ala A	la												
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Val A		•	•	3	•			1	.0				1	5
Trp I	le Pr	o Il . 2	e Le O	u As	n Se	r Gl	y Se	r Va	1 Le	u As	р Ту		e Se	r Glu
Arg S	er As	n Pr 5	o Ph	е Ту	r As	p Ar	g Th	г Су	s As	n As	n Gl 4		l Va	l Lys
Met G	ln Ar 50	g Le	u Th	r Le	u G1	u Hi: 5	s Le	i u Ası	n: G1:	n Me 6		1 Gl	y Il	e Glu
Tyr I	le Le	u Le	u Hi:	s Ala 70	a Gla	n Glu	ı Pr	o Ile	e Lei	u Ph		e Il	e Ar	
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Gln G	ln Ar	g Glı	n Sei 85	r Pro	Ala	a Glr	ı Va	l Ile 90	Pro	Let	ı Ala	a Ası	o Ty n 99	
Ile I	le Ala	100	v Val	Ile	Туз	Glr	i Ala 109	a Pro) Asp	Let	ı Gly	/ Sei		l Ile
Asn Se	r Arg	y Val	Leu	Thr	Ala	Val	His	Gly	Ile	G1r	Ser 125	Ala	Phe	Asp
Glu Al	a Met	Ser	Туг	Cys	Arg	Tyr	His	Pro	Ser	Lys 140		Туг	Trp	Trp
•••				ν,.					•					
His Ph	e Lys	Asp	His	Glu 150	Glu	Gln	Asp	Lys	Val 155	Arg	Pro	Lys	Ala	Lys 160
Arg Ly	s Glu	Glu	Pro 165	Ser	Ser	Ile	Phe	Gln 170	Arg	Gln	Arg	Val	Asp 175	Ala
Leu Le	u Leu	Asp	Leu	Arg	Gln	Lys	Phe	Pro	Pro	Lys	Phe			Leu '
Lys Pro	o Gly		Lys	Pro	Val	Pro	•		Gln	Thr	Lys	190 Lys	Glu	Ala
	193					200					205			
Glu Pro)	Pro	Glu	Thr	Val 215	Lys	Pro	Glu	Glu	Lys 220	Glu	Thr	Thr	Lys

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Ala Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr 210 220

Leu Lys Pro Gly Glu Lys Pro Val Pro Val Asp Gln Thr Lys Lys Glu

195 200

4.7 ×9. 185 € 1 × 1

205 🔯 🕮

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90
95

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Phe Cys Lys Lys Ser Tyr His Tyr Val Cys Ala Lys Lys Asp Gln Ala 115 120 125

Ile Leu Gln Val Asp Gly Asn His Gly Thr Tyr Lys Leu Phe Cys Pro 130 135 140

Glu His Ser Pro Glu Gln Glu Glu Ala Thr Glu Ser Ala Asp Asp Pro 145 150 155 160

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Leu Lys Lys Cys Gln Glu Ala Gly Leu Leu Thr Glu Leu Phe Glu His 210 215 220

Ile Leu Glu Asn Met Asp Ser Val His Gly Arg Leu Val Asp Glu Thr 225 230 235 240

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Gly Leu Phe Lys Asp Thr Leu Arg Lys Phe Gln Glu Val Ile Lys Ser 260 265 270

Lys Ala Cys Glu Trp Glu Glu Arg Gln Arg Gln Met Lys Gln Gln Leu 275 280 285

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Lys Met Gl 50	n Arg Leu	Thr Leu 55	Glu His	Leu Asn	Gln Met 60	Val Gly Il	ė
Glu Tyr Il 65	e Leu Leu	His Ala 70	Gln Glu	Pro Ile 75	Leu Phe	Ile Ile Ar	g 0
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1				5					10					15	•
	•				4.1		. :	÷ •							
Tyr	Lys	Ala	Thr	Val	Ala	Ser	Asp	Gln	Ile	Glu	Met	Asn	Arg	Leu	Lys
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23 a	Gin	T.011					Gln		Wal.	λla	Glu	Lau	Tim	202	T10
MIG	GIII		GIU	ASII	GIU	цуз		пуз	Val	ALC:			IYL	Ser	TIC
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	•					,	; :.	. •	1.5		15.7				25%
Ara	Lei			Glu			Glu								
	DCu	nsp	цуз	Giu	_	ALG	OIĢ	****	LCu		JCI	Jer	, Deu	GIII	
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Ala	Lvs	Val					Arg								
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	~1 -							•		•					
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	Giù	wah	GIU	Val		GIII	птэ	ALG			Lys	Dea	птэ	-	
145				•	150					155					160
			•									€.			: '3'
Leu	Ile	Ile	Ser	Asp	Leu	Glu	Asn	Thr	Val	Lys	Lys	Leu	Gln	Asp	Gln
				165					170				٠.	175	٠
					. +5 4:		a ()					., 5			
Taro	Wie	yen												•	Ara
пÃ2	nis	wah		GIU.	Arg	GIU	Ile	-	IIII	Leu	ura	Arg		Leu	ALG
			180					185					190		
• ·				٠٠.		-	. 😕 🖔		٠	- 1			٠.	٠.	
Glu	Glu	Ser	Ala	Glu	Trp	Arg	Gln	Phe	Gln	Ala	Asp	Leu	Gln	Thr	Ala
		195			-		200				_	205			
	Y														
1		:		_	- + /		_								
vai		rre	Ата	Asn	Asp		Lys	Ser	GIU	ALA		GIU	GIU	ше	GIY
	210		•			215					220				
	٠,٠	•										: ,		:	
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225		-1-	3	3	230					235	-1-			, _	240
					230					433					
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Pro Gln Asp Leu Pro Tyr Pro Asp Pro Ala Ile Ala Gln Phe Ser Val . 35 40 ---

Gln Lys Val Thr Pro Gln Ser Asp Gly Ser Ser Ser Lys Val Lys Val S 55 60.

Lys Val Arg Val Asn Val His Gly Ile Phe Ser Val Ser Ser Ala Ser . 65 70 75

Leu Val Glu Val His Lys Ser Glu Glu Asn Glu Glu Pro Met Glu Thr 90

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Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr 40 35 ·

Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln 50 55

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Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
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Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Gly
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Ser Gln Ala Gly Ser Lys Asp Lys Lys Met Asp Gln Pro Pro Gln Ala
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Lys Lys Ala Lys Val Lys Thr Ser Thr Val Asp Leu Pro Ile Glu Asn

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Asn Glu Gly Lys Met Ile Met Gln Asp Lys Leu Glu Lys Glu Arg Asn 115 120 125

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Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln 50 55 60

Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
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Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
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Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
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Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu 180 185 190

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				Gln 580					585					590		
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                                                                                                                  Phe Val Val Asn Phe
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 And State of The State of the State
   Val Ile Lys Gly Thr Met Val Ser Lys Phe Pro Val Ile Val Gly His
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Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu
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Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln
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Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu
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Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp
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Leu Pro Gly Val Val Ile Leu Ala Val Pro Ile Ala Leu Leu Val Tyr
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Phe Leu Ala Phe Asp Gln Lys Ser Tyr Phe Tyr Trp Ser Asn Phe Pro 65 70 75 80

Leu Pro Asn Val Glu Tyr Asn Ser Pro Phe Asn Ser Pro Ala Ser Pro 85 90 95

Gly Ile Pro

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Ser Pro Val Leu Thr Ser Glu Val His Ser Val Arg Ala Gly Arg His
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Leu Ala Thr Lys Leu Asn Ile Leu Val Gln Gln His Phe Asp Leu Ala 65 70 75 80

Ser Thr Thr Ile Thr Asn Ile Pro Met Lys Glu Glu Gln His Ala Asn 85 90 95

Thr Ser Ala Asn Tyr Asp Val Glu Leu Leu His His Lys Asp Ala His 100 105 110

Val Asp Phe Leu Lys Ser Gly Asp Ser His Leu Gly Gly Gly Ser Arg 115 120 125

Glu Gly Ser Phe Lys Glu Thr Ile Thr Leu Lys Trp Cys Thr Pro Arg 130 135 140

Thr Asn Asn Ile Glu Leu His Tyr Cys Thr Gly Ala Tyr Arg Ile Ser 145 150 155 160

Pro Val Asp Val Asn Ser Arg Pro Ser Ser Cys Leu Thr Asn Phe Leu 165 170 175 Leu Asn Gly Arg Ser Val Leu Leu Glu Gln Pro Arg Lys Ser Gly Ser 180 185 190

Lys Val Ile Ser His Met Leu Ser Ser His Gly Gly Glu Ile Phe Leu
195 200 205

His Val Leu Ser Ser Ser Arg Ser Ile Leu Glu Asp Pro Pro Ser Ile 210 215 220

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Arg Gly Lys Gly Glu Ile Thr Pro Ala Ala Ile Gln Lys Met Leu Asp 35 40 45

Asp Asn Asn His Leu Ile Gln Cys Ile Met Asp Ser Gln Asn Lys Gly
50 55 60

Lys Thr Ser Glu Cys Ser Gln Tyr Gln Gln Met Leu His Thr Asn Leu 65 70 75 80

Val Tyr Leu Ala Thr Ile Ala Asp Ser Asn Gln Asn Met Gln Ser Leu 85 90 95

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1					_		_	• •			9	DCu

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Asn Asn Glu Gln Leu Leu Val Asn Gln Gln Ala Ile Gln Ile Leu

Glu Lys Ile Ser Gln Pro Val Val Val Val Ala Ile Val Gly Leu Tyr
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Arg Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly Gln Asn His 65 70 75 80

Gly Phe Pro Leu Gly Ser Thr Val Glm Ser Glu Thr Lys Gly Ile Trp 85 90 95

Met Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu
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Leu Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn 115 120 125

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Lys Ile Ser Gln Pro Val Val Val Val Ala Ile Val Gly Leu Tyr Arg
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Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly Gln Asn His Gly 50 55 60

Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr Lys Gly Ile Trp Met 65 70 75 80

Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu Leu

85 90 95

Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn Asp 100 105 110

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Ile Asn Asp Pro Phe Ile Asp Leu Asn Tyr Met Val Tyr Met Phe Gln
35 40 45

Tyr Asp Ser Thr His Gly Lys Phe His Gly Thr Val Glu Ala Glu Asn

Gly Lys Leu Val Ile Asn Gly Asn Pro Ile Thr Ile Phe Gln Glu Arg
65 70 75 80

Asp Pro Ser Lys Ile Lys Trp Gly Asp Ala Gly Ala Glu Tyr Val Val 85 90 95

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20 25 30
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Val Ala Ile Asn Asp Pro Phe Ile Asp Leu Asn Tyr Met Val Tyr Met 50 60

Phe Gln Tyr Asp Ser Thr His Gly Lys Phe His Gly Thr Val Glu Ala 65 70 75 80

Glu Asn Gly Lys Leu Val Ile Asn Gly Asn Pro Ile Thr Ile Phe Gln 85 90 95

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Gln	Glu	Phe 35	. Val	Trp	Asp	Tyr	Val		Leu	Asp	Glu	Ala 45		Lys	Ile
Lys	Thr 50		Ser	Thr	Lys	Ser 55		Ile	Cys	Ala	Arg 60		Ile	Pro	Ala
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Glu	Leu	Trp	Ser	Leu 85		Asp	Phe	Ala	Cys 90		Gly	Ser	Leu	Leu 95	_
			Thr 100					105	-				110		
		115			1		120	-			•	125			
	130		Leu			135					140			•	
145	-	 			150	₩.**\	3.			155	٠			•	160
	35,3	2.	Asn	165	737	7.	TV.		170	7	· .			175.	
	Ť.,	. • •	Asn 180		٠.	12	',∕0 4 [°]	185	· · · · ·	1.7	-		190		
	• • •	195		5/1	. %. े		200	* .	•		:	205			
	210	Alan	Thr		4,50	215	```	. 🐔	x:	ξ.	220	٠.			-
Leu 225	Cys	Asp একট এ	His	Pro	Arg 230 .	Leu	Leu		Ala			Суз	Cys		Leu 240
Asn	Leu	_	Thr	Phe 245	Ser	Ala			٠.				s Pap Ngjar		
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Arg Ser Glu Thr Ser Va	l Pro Asp 55	His Val Val	Trp Ser Leu Phe Asn
Thr Leu Phe Met Asn Pr	o Cys Cys 0	Leu Gly Phe	Ile Ala Phe Ala Tyr
Ser Val Lys Ser Arg As 85	,	Met Val Gly	
Gln Ala Tyr Ala Ser Th	r Ala Lys	90 Cys Leu Asn	95 Ile Trp Ala Leu Ile
100		105	110
Leu Gly Ile Leu Met Th	r Ile Leu 120	Leu Ile Val	Ile Pro Val Leu Ile 125
Phe Gln Ala Tyr Gly 130	•		
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1 5		10	
		10	15
Ser Thr Pro Gly Thr Ala	Pro Pro	- V	
Ser Thr Pro Gly Thr Ala 20	Pro Pro	- V	
20		Pro Lys Val 1	Leu Thr Ser Pro Ala 30
Thr Thr Pro Met Ser Thr	Met Ser	Pro Lys Val 1 25 Thr Ile His 1	Leu Thr Ser Pro Ala 30 Thr Ser Ser Thr Pro 45
Thr Thr Pro Met Ser Thr 35 Glu Thr Thr His Thr Ser	Met Ser	Pro Lys Val 1 25 Thr Ile His :	Leu Thr Ser Pro Ala 30 Thr Ser Ser Thr Pro 45
Thr Thr Pro Met Ser Thr	Met Ser 140 Thr Val 155	Pro Lys Val 1 25 Thr Ile His :	Chr Ser Ser Thr Pro 45 Thr Ala Thr Met Thr 60
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Thr Thr Pro Met Ser Thr 35 Glu Thr Thr His Thr Ser 50 Arg Ala Thr Asn Ser Thr 65 70 Arg Ile Leu Thr Glu Leu 85 Gly Ser Thr Ala Thr Leu 100 Thr Glu Pro Ser Thr Ile 115 Ala Thr Ala Ser Ser Thr	Met Ser 1 40 Thr Val I 55 Ala Thr I Ser Ser I 1 Ala Thr V 120 Leu Gly T 135	Pro Lys Val 1 25 Thr Ile His 1 Pro Ser Ser 1 75 Thr Ala Thr 1 90 Thr Pro Gly T 05 That Ala His T	Chr Ser Ser Thr Pro 45 Chr Ala Thr Met Thr 60 Chr Leu Gly Thr Thr 80 Chr Thr Ala Alâ Thr 95 Chr Thr Gly Ser Thr 125 Chr Pro Lys Val Val

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                                             化基环烷酸镁 经证券证据
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<213> homo sapien

9年 1百年7 11日代

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	gt	-				242
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	ggcc	-300032-			•	424
	9900					724
	<210> 138		3. A. O.	**** * * * * * * * * * * * * * * * * * *	$(1,8) \rightarrow (1,8) \times (1,8) \times (1,8)$	
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		geoggeeg	•		4 = 4	
	<210> 139	. *			, raking terminan	
	<211> 510				Mar. 1945 (#12.55)	
	<212> DNA					
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	and bupie	•••			migraphic of the control of the cont	
	<400> 139	•			renale as to	
•	gaatteggea egaggtteeg	tacaactcac	ададаадсда	atggagaaa	tragraagta .	60
	ccccaaggag ctgcgcaagt					120
						180
	gtgccagcgc cggacccgtt					240
	tgctgcaact acatcacaga		•••			300
	caggagtaac ctggatgagg		-, -	_		360
	cccagagage tggctgtgga					420
	tacgaagete atgaatatat					
	gagcatgtcg gacaagaaag		ggcagacccc			480
	ggacttette ategacetge	gyctacccta	* * * ***	or the second	and the property of	510
	<210> 140	٠.	1.7		STANKER ST	
				·	100 miles 2000 miles	
	<211> 360		• • • •	. Barbara	water to the	
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tetgagtgga aggecaetga aagteaagga agateetgat ggtgaacatg caaggagage

. 341.

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904 -

114

111117. 11115.

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4. 11.

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44.

1...3.05

148

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                                                                       180
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                                                                       300
cetectgice cagegagage aggaaatagt ggicetgeag cageaactge aggaageeag
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cctagcccag ag
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                                                                      360
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                                                                      360
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                                                                     240
aagaattgaa aaaggettat aggaaactgg cettgaagta ceateetgat aagaaceeaa
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aaagggaatt atatgacaaa ggaggagaac aggcaattaa agagggtgga gcaggtggcg
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gttttggctc ccccatggac atctttgata tgttttttgg aggaggagga aggatgcaga
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                                                                     300
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893
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                         HISTORIUM AT ME
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                        被关系统一。在
      <213> homo sapien
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                                                                     190
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                                                                     300
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                                                                     420
                                                                     480
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                                                                     480
                                                                     540
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                                                                     720
                                                                     780
getetaetta cagaacagee etgaggeetg tgaetatggg etetgaaggg ggcaggagte:
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14.36

18

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3393

335.4

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08

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 gcgggcggtc accggctacc gtgaccccta caccgagcag accatctcgc tcttccaggc
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	cectadyye gaayyayaac gaccege	tca gaatqaqaad	I aggaaggaga	AAAACataaa	180
	adyayyayyc aatcgctttg agccata	tgc caatccaact	aaaagaraca	gaggettest	240
•	cacadacaca contendand Edagate	gca qtcacttaaa	Lgacctggtta	2202222200	300
	cygradyca acatacytyg agetett	aat qqacqctqaa	ggaaagtcaa	agagatataa	360
	Lyctyctyda ttcaagatgg aagagag	cat qaaaaaagct	GCGGBAGTCC	taaacaacca .	420
	tagectgage ggaagaccae tgaaagtg	caa aqaaqatcct	gatggtgaac	2100020000	480
	ageactical additioned craceact	gg tgggatgggt	atgggaccag	gtggcccagg	540
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	cyayyccarc cragccarce acaaqqaq	GC CCagaggatc	octoagages	accacat cas	180
	accarragge agradecer acaccacc	qt caccccccaa	atcatcaact	CCBBatagga	240
	Aggadinacad caderaged cagaged	ga ccataccctc	Ctonaggagg	202002200	. 300
	acadecease dadeaccede decedes	tt coccaoccao	gccaatgttg	tagggggggta	360
	garrrayarr aagarggagg agarcggg	CG Catctccatt	gagatgaacg	aaaccataaa	420
	agaccagcig agccacctga agcagtat	da acocaocato	OTOGACTACE	2000002000	480
	agacetycty gaycagcage accadete	at ccaggaggcc	CtCatCttCC	20220220	540
	caccaactat accatggage acatecge	gt gggctgggag	Cagctoctca	ccaccattee	600
	ccgg				604
_	<u>a kanada</u> ja kanada ka		ration to		004
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	aggcgaaaga gtggatggca acagtctaa	t totaggarar	Otaataggaa (reggeacaa	•
	taccccaggg cccgcataca gtggtcgag	a gacaatatac	ccaataggaa (ccaacaage	180
	ccagaacgtc acccagaatg acacaggat	t cratacceta	cecaalytal (ceigeigat	240
	tgtgaatgaa gaagcaaccg gacagttco	a totataccca	caagicalaa a	gccagatet	300
	ctecagcaac aactccaacc ccgtggagg	a casocatory	yaycigcca a	gccctccat	360
	tgaggttcag aacacaacct acctor	a caayyatyct (grggccttca c	ctgtgaacc	420
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                                                                         240
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493

ē.,

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Lys Met Glu Glu Glu Ser Gly Ala Pro Cys Val Pro Ser Gly Asn Gly Ala Pro Gly Pro Lys Gly Glu Glu Arg Pro Thr Gln Asn Glu Lys Arg 40 45 Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr Ser 60 Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe Asp 70 Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly Glu 85 90 Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg Gly 105 Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala Ala 120 125 Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val Lys ¥. 135 140 Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Ala Gly -- 150 155 Arg Leu Gly Ser Thr Val Phe Val Ala Asn Leu Asp Tyr Lys Val Gly 165 170 175 Trp Lys Lys Leu Lys Glu Val Phe Ser Met Ala Gly Val Val Val Arg 185 180 190 Ala Asp Ile Leu Glu Asp Lys Asp Gly Lys Ser Arg Gly Ile Gly Ile 200 195 Val Thr Phe Glu Gln Ser Ile Glu Ala Val Gln Ala Ile Ser Met Phe 210 215 220 Asn Gly Gln Leu Leu Phe Asp Arg Pro Met His Val Lys Met Asp Glu 230 ` 235 Arg Ala Leu Pro Lys Gly Asp Phe Phe Pro Pro Glu Arg His Ser 250

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<213> Homo sapien

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 Asp Phe Lys
 Gly Gly Leu Asn Gly Ala Val
 Tyr Leu Pro Ser Lys
 Glu

 145
 150
 155
 160

 Leu Asp Tyr Leu Ile Lys Phe Ser Lys
 Leu Thr Cys
 Pro Glu Arg
 Asn

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 Glu Ser Leu Arg Gln
 Thr Leu Glu Gly Ser
 Thr Val

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Met Gln Glu Ser Val Leu Asp Phe Asp Lys Pro Ser Ser Ala Ile Pro 340 345 Thr Ser Gln Pro Pro Ser Ala Thr Pro Gly Ser Pro Val Ala Ser Lys 355 360 Glu Gln Asn Leu Ser Ser Gln Ser Asp Phe Leu Gln Glu Pro Leu Gln 375 380 Val Phe Asn Val Asn Ala Pro Leu Pro Pro Arg Lys Glu Gln Glu Ile 390 395 Lys Glu Ser Pro Tyr Ser Pro Gly Tyr Asn Gln Ser Phe Thr Thr Ala 405 410 Ser Thr Gln Thr Pro Pro Gln Cys Gln Leu Pro Ser Ile His Val Glu 420 425 Gln Thr Val His Ser Gln Glu Thr Ala Ala Asn Tyr His Pro Asp Gly 435 440 445 Thr Ile Gln Val Ser Asn Gly Ser Leu Ala Phe Tyr Pro Ala Gln Thr 455 460 Asn Val Phe Pro Arg Pro Thr Gln Pro Phe Val Asn Ser Arg Gly Ser 470 475 Val Arg Gly Cys Thr Arg Gly Gly Arg Leu Ile Thr Asn Ser Tyr Arg 485 490 Ser Pro Gly Gly Tyr Lys Gly Phe Asp Thr Tyr Arg Gly Leu Pro Ser 495 500 505 510 Ile Ser Asn Gly Asn Tyr Ser Gln Leu Gln Phe Gln Ala Arg Glu Tyr 520 Y 525 Ser Gly Ala Pro Tyr Ser Gln Arg Asp Asn Phe Gln Gln Cys Tyr Lys 530 535 ... 540 Arg Gly Gly Thr Ser Gly Gly Pro Arg Ala Asn Ser Arg Ala Gly Trp 550 555 Ser Asp Ser Ser Gln Val Ser Ser Pro Glu Arg Asp Asn Glu Thr Phe 565 570 575 Asn Ser Gly Asp Ser Gly Gln Gly Asp Ser Arg Ser Met Thr Pro Val 580 585 Asp Val Pro Val Thr Asn Pro Ala Ala Thr Ile Leu Pro Val His Val 590 600 . 605 Tyr Pro Leu Pro Gln Gln Met Arg Val Ala Phe Ser Ala Ala Arg Thr 615 620 Ser Asn Leu Ala Pro Gly Thr Leu Asp Gln Pro Ile Val Phe Asp Leu 625 630 635 Leu Leu Asn Asn Leu Gly Glu Thr Phe Asp Leu Gln Leu Gly Arg Phe 645 650 Asn Cys Pro Val Asn Gly Thr Tyr Val Phe Ile Phe His Met Leu Lys 660 665 Leu Ala Val Asn Val Pro Leu Tyr Val Asn Leu Met Lys Asn Glu Glu . 680 675 Val Leu Val Ser Ala Tyr Ala Asn Asp Gly Ala Pro Asp His Glu Thr 695 700 Ala Ser Asn His Ala Ile Leu Gln Leu Phe Gln Gly Asp Gln Ile Trp 705 710 715 Leu Arg Leu His Arg Gly Ala Ile Tyr Gly Ser Ser Trp Lys Tyr Ser 725 730 Thr Phe Ser Gly Tyr Leu Leu Tyr Gln Asp

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 Ile Gln Ala Val Glu Arg Arg Gly Val Gly Ala Met Glu Ile Val Ala
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Met Asp Met Lys Leu Arg Gly Met Tyr Ile Ala Arg Gln Leu Ser Phe
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                                         460
Thr Gly Val Thr Phe Lys Ile Glu Glu Val Leu Leu Ser Gln Ser Tyr
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Val Lys Met Tyr Asn Lys Ala Val Lys Leu Trp Val Ile Ala Arg Glu
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Arg Phe Gln Gln Ala Ala Asp Leu Ile Asp Ala Glu Gln Arg Met Lys
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Lys Ser Met Trp Gly Gln Phe Trp Ser Ala His Gln Arg Phe Phe Lys
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Tyr Leu Cys Ile Ala Ser Lys Val Lys Arg Val Val Gln Leu Ala Arg
530 535 540
Glu Glu Ile Lys Asn Gly Lys Cys Val Val Ile Gly Leu Gln Ser Thr
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Gly Glu Ala Arg Thr Leu Glu Ala Leu Glu Glu Gly Gly Glu Leu
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Asn Asp Phe Val Ser Thr Ala Lys Gly Val Leu Gln Ser Leu Ile Glu
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                                     590
Lys His Phe Pro Ala Pro Asp Arg Lys Lys Leu Tyr Ser Leu Leu Gly
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Ile Asp Leu Thr Ala Pro Ser Asn Asn Ser Ser Pro Arg Asp Ser Pro
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Cys Lys Glu Asn Lys Ile Lys Lys Arg Lys Gly Glu Glu Ile Thr Arg
                 630
                                   635 640
Glu Ala Lys Lys Ala Arg Lys Val Gly Gly Leu Thr Gly Ser Ser Ser
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Asp Asp Ser Gly Ser Glu Ser Asp Ala Ser Asp Asn Glu Glu Ser Asp
          660
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Tyr Glu Ser Ser Lys Asn Met Ser Ser Gly Asp Asp Asp Phe Asn
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Pro Phe Leu Asp Glu Ser Asn Glu Asp Asp Glu Asn Asp Pro Trp Leu
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Ile
705
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Gly	Glu	Asp		Arg	Glu	Leu	Gly	Ser	Ser	Pro	His	Asp	Arg	Gly	Ala
_	_	_	100	_		-	a 3			a	(Tille and	a1 -		6	C1
Ser.	Pro	Arg 115	Asp	Leu	Ser	GIY	Glu 120	ser	Pro	Cys	inr	125	Arg	ser	GIÀ
Leu	Leu	Pro	Glu	Arg	Arg	Gly	Asp	Ser	Pro	Trp	Pro	Pro	Trp	Pro	Ser.
. ,	130			•		135	_			٠.	140				٠,
Pro		Glu	Ara	Asn	Ala	Glv	Thr	Ara	Asp	Arg	Glu	Glu	Ser	Pro	Arq
145			3		150	- J.E.		3		155	4.77				160
	Tra	Glv.	Glv	Δla		Ser	Pro	Ara	Glv		Glu	Ala	Glv	Pro	Arg
rap.	ııp.	OLY	017	165	0		: 31	:5	170			7.7.	3 2	175	
01	T	C114	D=0		Drice	Car	G1y	บเล		Aen	Giv	Dro	Ard	Ara	Arm
GIU	пр	GTĀ		Ser.	FEO	Ser	Gly	185	GLy	Map	Oly	110	190	*****	,49
_			180	•	03				٠	W	OÎ	المشارة	130	111.0	C1.
Pro	Arg	_	Arg	arg	GIY	Arg	Lys	GIY	Arg	Mec	GIY		GIII	ura	GIU
		195				٠.	200					205			
		Ala	Thr	Ala			Ala	Ala.	Thr	Ala	Thr	Gly	GIA	Inr	ALA
١. ٠	210		•			215,					220				5 5 50
Glu	Glu.	Ala	Gly	Ala	Ser	Ala	Pro	Glu	Ser	Gln	Ala	Gly	Gly	Gly	Pro
225					230	3				235			· .		240
Arg	Gly	Arg	Ala	Arg	Gly	Pro	Arg	Gln	Gln	Gly	Arg	Arg	Arg	His	Gly
				245			.43.4		250		•	,		,255	
Thr:	Gln	Arg	Arg	Arg	Gly	Pro	Pro	Gln	Ala	Arg	Glu	Glu	Gly	Pro	Arg
,			260	•				265					270		
Asp	Ala	Thr	Thr	Ile	Leu	Gly	Leu	Gly	Thr	Pro	Ser	Gly	Glu	Gln	Arg
•		275			ĝ.	_	280	_				285	, .	· · · · · ·	.e .eest
Ala	Asp	Gln	Ser	Gln	Ala	Leu	Pro	Ala	Leu	Ala	Gly	Ala	Ala	Ala	Ala
	290	V				295					300				F. 5
		ніа	Ala	TIA	Pro		Ala	Ğlv	Pro	Ala		Ala	Pro	Val	Glv
			. ALG		310	0.2	****	O17		315	,				320
			2	2-0		Cly	Trp	Arre	Gly		Arci	Arm	ČIŸ	ัดโซ	Ser
GLY.	ALG	GIY		325		GIJ	110	<i></i>	220	Ų-1				335	-,
	<u></u>	.27.0				Glar	Arg	761v	Glv	Àrœ	Gly	Ara	ัดโช		Glv
MIG	GLY.	ALG	340		Grå	Gry	ΑĽ	345	GLY	wa	GIJ	AL 9	350		
~3					G1	@1.4			N	C1		61.7		A1 =	GIV
GIA:	GIY.		GIY	GIA	GIĀ	GIY	Ala	GTÅ	Arg	GLY	GIY		WIG	ALG.	GLY
	`	355			_		360	~ 3				365		~1-	B
Pro		Glu	Gly	Ala	Ser		Pro	GIY	ATS	arg		GIY	GTĤ	GIN	Arg
	370					375				•	380			_	
Arg	Arg	Gly	Arg	Gly	Pro	Pro	Ala	Ala	Gly		Ala	GIU	Val	ser	
385					390					395			172.0	والمعارين والم	400
Arg	Gly	Arg	Arg	Ala	Arg	Gly	Gln	Arg	Ala	Gly	Glu	Glu	Ala	Gln	Asp
				405					410					415	
Gly	Leu	Leu	Pro	Arg	Gly	Arg	Asp	Arg	Leu	Pro	Leu	Àrğ	Pro	Gly	Asp
			420					425					430		
Ala	Asn	Gln	Arq	Ala	Glu	Arg	Pro	Gly	Pro	Pro	Arg	Gly	Gly	His	Gly
		435	. –				440		, ·			445	12		
Pro				Ser	Ser	Ala	Pro		Thr	Ser	Pro	Pro	Ara	His	Pro
	450					455					460		3		
			VAI					Gl n	A	T.e.		λτα	Ġln.	Pho	Ara
		тър	AGT	Ser			Arg	Gin		475	112	~-9	-	· · · ·	Arg 480
465		٥.		-	470			D			B	D	Desc	×12 -	
val	GIÅ	GIA	GIA		PIO	PTO	Pro	PTO			Arg	Pro	PLO		AGT
_	_	_		485	_	-	• • •	_	490			D	63	495	ma.
Leu	Leu	Pro			arg		Ala		ALa	GIA	ASP	PTO		WIG	Tur
			500	•				505					510		

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                   520
                            525
Pro Arg Arg Pro Asp Pro Ala Ala Pro Ser Glu Glu Gly Leu Arg Met
                   535
                                     540 ·
Glu Ser Ser Val Asp Asp Gly Ala Thr Ala Thr Thr Ala Asp Ala Ala
                550
                           555
Ser Gly Glu Ala Pro Glu Ala Gly Pro Ser Pro Ser His Ser Pro Thr
             565
                           570
Met Cys Gln Thr Gly Gly Pro Gly Pro Pro Pro Pro Gln Pro Pro Arg
                          585 590
Trp Leu Pro
      595
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<210> 188 <211> 376 <212> PRT

<213> Homo sapien

<400> 188 Glu Met Arg Lys Phe Asp Val Pro Ser Met Glu Ser Thr Leu Asn Gln 5 10 10 15 Pro Ala Met Leu Glu Thr Leu Tyr Ser Asp Pro His Tyr Arg Ala His 20 25 30 Phe Pro Asn Pro Arg Pro Asp Thr Asn Lys Asp Val Tyr Lys Val Leu 40 Pro Glu Ser Lys Lys Ala Pro Gly Ser Gly Ala Val Phe Glu Arg Asn 55 m 60 m Glý Pro His Ala Ser Ser Ser Gly Val Leu Pro Leu Gly Leu Gln Pro 80 Ala Pro Glý Leu Ser Lys Ser Leu Ser Ser Gln Val Trp Gln Pro Ser 85 90. Pro Asp Pro Trp His Pro Gly Glu Gln Ser Cys Glu Leu Ser Thr Cys 100 105 110 Arg Gln Gln Leu Glu Leu Ile Arg Leu Gln Met Glu Gln Met Gln Leu 120 and the grade of 125 of the contract of the Gln Asn Gly Ala Met Cys His His Pro Ala Ala Phe Ala Pro Leu Leu 135 July 10 10 140 to 16 1 1 1 1 Pro Thr Leu Glu Pro Ala Gln Trp Leu Ser Ile Leu Asn Ser Asn Glu . . 150 155 His Leu Leu Lys Glu Leu Leu Ile Asp Lys Gln Arg Lys His .. . 165 170 Sec. (175 Ile Ser Gln Leu Glu Gln Lys Val Arg Glu Ser Glu Leu Gln Val His 180 185 - He gate v. 190 . . Ser Ala Leu Leu Gly Arg Pro Ala Pro Phe Gly Asp Val Cys Leu Leu 200 205 Arg Leu Gln Glu Leu Gln Arg Glu Asn Thr Phe Leu Arg Ala Gln Phe 210 215 220 Ala Gln Lys Thr Glu Ala Leu Ser Lys Glu Lys Met Glu Leu Glu Lys 230 235 Lys Leu Ser Ala Ser Glu Val Glu Ile Gln Leu Ile Arg Glu Ser Leu 245 250 Lys Val Thr Leu Gln Lys His Ser Glu Glu Gly Lys Lys Gln Glu Glu 260 265 Arg Val Lys Gly Arg Asp Lys His Ile Asn Asn Leu Lys Lys Lys Cys

```
Gln Lys Glu Ser Glu Gln Asn Arg Glu Lys Gln Gln Arg Ile Glu Thr
                   295
                                   300
Leu Glu Arg Tyr Leu Ala Asp Leu Pro Thr Leu Glu Asp His Gln Lys
             310
                               315
Gln Thr Glu Gln Leu Lys Asp Ala Glu Leu Lys Asn Thr Glu Leu Gln
        325
                    . . . .
                            330
Glu Arg Val Ala Glu Leu Glu Thr Leu Leu Glu Asp Thr Gln Ala Thr
                              350
         340
                      345
Cys Arg Glu Lys Glu Val Gln Leu Glu Ser Leu Arg Gln Arg Glu Ala
 355
                      360
Asp Leu Ser Ser Ala Arg His Arg
   370
                   375
     <210> 189
     <211> 160
     <212> PRT
     <213> Homo sapien
     <400> 189
Met Leu Glu Ala His Arg Arg Gln Arg His Pro Phe Leu Leu Gly
   Thr Thr Ala Asn Arg Thr Gln Ser Leu Asn Tyr Gly Cys Ile Val Glu
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Asn Pro Gln Thr His Glu Val Leu His Tyr Val Glu Lys Pro Ser Thr

35
40
45

Phe Ile Ser Asp Ile Ile Asn Cys Gly Ile Tyr Leu Phe Ser Pro Glu
50
55
60

Ala Leu Lys Pro Leu Arg Asp Val Phe Gln Arg Asn Gln Gln Asp Gly
65
70
75
80

Gln Leu Glu Asp Ser Pro Gly Leu Trp Pro Gly Ala Gly Thr Ile Arg
85
90
95

Leu Glu Gln Asp Val Phe Ser Ala Leu Ala Gly Gln Gly Gln Ile Tyr
100
105

Val His Leu Thr Asp Gly Ile Trp Ser Gln Ile Lys Ser Ala Gly Ser

Pro Glu Arg Leu Ala Lys His Thr Pro Gly Gly Pro Trp Ile Arg Gly 145 150 155 160

<210> 190 <211> 146 <212> PRT

<213> Homo sapien

<400> 190 :

 Met Asp Pro Arg Ala Ser Leu Leu Leu Leu Gly Asn Val Tyr Île His

 1
 5
 10
 15

 Pro Thr Ala Lys Val Ala Pro Ser Ala Val Leu Gly Pro Asn Val Ser
 20
 25
 30

 Ile Gly Lys Gly Val Thr Val Gly Glu Gly Val Arg Leu Arg Glu Ser
 45

 Ile Val Leu His Gly Ala Thr Leu Gln Glu His Thr Cys Val Leu His
 50
 60

 Ser Ile Val Gly Trp Gly Ser Thr Val Gly Arg Trp Ala Arg Val Glu

65 70 75 75 80

Gly Thr Pro Ser Asp Pro Asn Pro Asn Asp Pro Arg Ala Arg Met Asp 85 90 95

Ser Glu Ser Leu Phe Lys Asp Gly Lys Leu Leu Pro Ala Ile Thr Ile 100 105 110

Leu Gly Cys Arg Val Arg Ile Pro Ala Glu Val Leu Ile Leu Asn Ser 115 120 125

Ile Val Leu Pro His Lys Glu Leu Ser Arg Ser Phe Thr Asn Gln Ile 130 135 140

<210> 191 <211> 704 <212> PRT <213> Homo sapien

<400> 191

Glu Gly Gly Cys Ala Ala Gly Arg Gly Arg Glu Leu Glu Pro Glu Leu 1 5 10 Glu Pro Gly Pro Gly Pro Gly Ser Ala Leu Glu Pro Gly Glu Glu Phe 20 Glu Ile Val Asp Arg Ser Gln Leu Pro Gly Pro Gly Asp Leu Arg Ser 30 35 ... # 40 45 Ala Thr Arg Pro Arg Ala Ala Glu Gly Trp Ser Ala Pro Ile Leu Thr
50 55 60 Leu Ala Arg Arg Ala Thr Gly Asn Leu Ser Ala Ser Cys Gly Ser Ala 65 70 75 Leu Arg Ala Ala Gly Leu Gly Gly Gly Asp Ser Gly Asp Gly Thr 95 90 Ala Arg Ala Ala Ser Lys Cys Gln Met Met Glu Glu Arg Ala Asn Leu 100 105 Met His Met Met Lys Leu Ser Ile Lys Val Leu Leu Gln Ser Ala Leu .. 115 120 Ser Leu Gly Arg Ser Leu Asp Ala Asp His Ala Pro Leu Gln Gln Phe 135 Phe Val Val Met Glu His Cys Leu Lys His Gly Leu Lys Val Lys Lys 150 155 160 Ser Phe Ile Gly Gln Asn Lys Ser Phe Phe Gly Pro Leu Glu Leu Val 165 170 Glu Lys Leu Cys Pro Glu Ala Ser Asp Ile Ala Thr Ser Val Arg Asn 180 185 190 Leu Pro Glu Leu Lys Thr Ala Val Gly Arg Gly Arg Ala Trp Leu Tyr 200 205 Leu Ala Leu Met Gln Lys Lys Leu Ala Asp Tyr Leu Lys Val Leu Ile 215 220 Asp Asn Lys His Leu Leu Ser Glu Phe Tyr Glu Pro Glu Ala Leu Met 230 235 240 Met Glu Glu Gly Met Val Ile Val Gly Leu Leu Val Gly Leu Asn 245 250 Val Leu Asp Ala Asn Leu Cys Leu Lys Gly Glu Asp Leu Asp Ser Gln 260 265 Val Gly Val Ile Asp Phe Ser Leu Tyr Leu Lys Asp Val Gln Asp Leu 280 285 Asp Gly Gly Lys Glu His Glu Arg Ile Thr Asp Val Leu Asp Gln Lys

295 300 Asn Tyr Val Glu Glu Leu Asn Arg His Leu Ser Cys Thr Val Gly Asp 310 315 Leu Gln Thr Lys Ile Asp Gly Leu Glu Lys Thr Asn Ser Lys Leu Gln 325 330 335 Glu Glu Leu Ser Ala Ala Thr Asp Arg Ile Cys Ser Leu Gln Glu Glu 340 345 Gln Gln Gln Leu Arg Glu Gln Asn Glu Leu Ile Arg Glu Arg Ser Glu Lys Ser Val Glu Ile Thr Lys Gln Asp Thr Lys Val Glu Leu Glu Thr 365 375 380 Tyr Lys Gln Thr Arg Gln Gly Leu Asp Glu Met Tyr Ser Asp Val Trp 390 395 Lys Gln Leu Lys Glu Glu Lys Lys Val Arg Leu Glu Leu Glu Lys Glu 405 410. Leu Glu Leu Gln Ile Gly Met Lys Thr Glu Met Glu Ile Ala Met Lys 420 425 Leu Leu Glu Lys Asp Thr His Glu Lys Gln Asp Thr Leu Val Ala Leu 435 440 Arg Gln Gln Leu Glu Glu Val Lys Ala Ile Asn Leu Gln Met Phe His 455 Lys Ala Gln Asn Ala Glu Ser Ser Leu Gln Gln Lys Asn Glu Ala Ile 470 475 Thr Ser Phe Glu Gly Lys Thr Asn Gln Val Met Ser Ser Met Lys Gln 485 490 Met Glu Glu Arg Leu Gln His Ser Glu Arg Ala Arg Gln Gly Ala Glu 505 Glu Arg Ser His Lys Leu Gln Gln Glu Leu Gly Gly Arg Ile Gly Ala 515 520 Leu Gln Leu Gln Leu Ser Gln Leu His Glu Gln Cys Ser Ser Leu Glu 530 ٠, 535 540 Lys Glu Leu Lys Ser Glu Lys Glu Gln Arg Gln Ala Leu Gln Arg Glu 545 550 **5**55 Leu Gln His Glu Lys Asp Thr Ser Ser Leu Leu Arg Met Glu Leu Gln
565 570 575 Gln Val Glu Gly Leu Lys Lys Glu Leu Arg Glu Leu Gln Asp Glu Lys 580 585 Ala Glu Leu Gln Lys Ile Cys Glu Glu Glu Glu Gln Ala Leu Gln Glu
595 600 605 Met Gly Leu His Leu Ser Gln Ser Lys Leu Lys Met Glu Asp Ile Lys 610 615 620 Glu Val Asn Gln Ala Leu Lys Gly His Ala Trp Leu Lys Asp Asp Glu ٠. 630 635 Ala Thr His Cys Arg Gln Cys Glu Lys Glu Phe Ser Ile Ser Arg Arg · 645 650 Lys His His Cys Arg Asn Cys Gly His Ile Phe Cys Asn Thr Cys Ser 660 665 Ser Asn Glu Leu Ala Leu Pro Ser Tyr Pro Lys Pro Val Arg Val Cys 675 680 Asp Ser Cys His Thr Leu Leu Gln Arg Cys Ser Ser Thr Ala Ser 695

<210> 192
<211> 331
<212> PRT

<213> Homo sapien

<400> 192 Arg Ala Gly Ala Ser Ala Met Ala Leu Arg Lys Glu Leu Leu Lys Ser - 1 10 . 15 Ile Trp Tyr Ala Phe Thr Ala Leu Asp Val Glu Lys Ser Gly Lys Val Ser Lys Ser Gln Leu Lys Val Leu Ser His Asn Leu Tyr Thr Val Leu 40 His Ile Pro His Asp Pro Val Ala Leu Glu Glu His Phe Arg Asp Asp 55 60 Asp Asp Gly Pro Val Ser Ser Gln Gly Tyr Met Pro Tyr Leu Asn Lys 70 80 75 Tyr Ile Leu Asp Lys Val Glu Glu Gly Ala Phe Val Lys Glu His Phe 85 90 Asp Glu Leu Cys Trp Thr Leu Thr Ala Lys Lys Asn Tyr Arg Ala Asp 100 105 Ser Asn Gly Asn Ser Met Leu Ser Asn Gln Asp Ala Phe Arg Leu Trp 115 . 120 125 Cys Leu Phe Asn Phe Leu Ser Glu Asp Lys Tyr Pro Leu Ile Met Val 130 135 140 Pro Asp Glu Val Glu Tyr Leu Leu Lys Lys Val Leu Ser Ser Met Ser 145 155 160 150 Leu Glu Val Ser Leu Gly Glu Leu Glu Glu Leu Leu Ala Gln Glu Ala 165 170 175 👘 🧻 Gln Val Ala Gln Thr Thr Gly Gly Leu Ser Val Trp Gln Phe Leu Glu 180 185 Leu Phe Asn Ser Gly Arg Cys Leu Arg Gly Val Gly Arg Asp Thr Leu 195 200 205 Ser Met Ala Ile His Glu Val Tyr Gln Glu Leu Ile Gln Asp Val Leu 210 215 220 Lys Gln Gly Tyr Leu Trp Lys Arg Gly His Leu Arg Arg Asn Trp Ala 225 230 235 240. Glu Arg Trp Phe Gln Leu Gln Pro Ser Cys Leu Cys Tyr Phe Gly Ser 245 250 255 Glu Glu Cys Lys Glu Lys Arg Gly Ile Ile Pro Leu Asp Ala His Cys 260 265 270 Cys Val Glu Val Leu Pro Asp Arg Asp Gly Lys Arg Cys Met Phe Cys 275 280 285 Val Lys Thr Ala Thr Arg Thr Tyr Glu Met Ser Ala Ser Asp Thr Arg .295 ٠. * 300 Gln Arg Gln Glu Trp Thr Ala Ala Ile Gln Met Ala Ile Arg Leu Gln 305 310 315 Ala Glu Gly Lys Thr Ser Leu His Lys Asp Leu. 325

<210> 193 <211> 475 <212> PRT <213> Homo sapien

<400> 193

Lys Asn Ser Pro Leu Leu Ser Val Ser Ser Gln Thr Ile Thr Lys Glu

1 5 10 15

Asn Asn Arg Asn Val His Leu Glu His Ser Glu Gln Asn Pro Gly Ser

			20					25					30		
Ser	Ala	Gly 35	Asp	Thr	Ser	Ala	Ala 40	His	Gln	Val	Val	Leu 45	Gly	Glu	Asn
Leu	Ile 50	Ala	Thr	Ala	Leu	Cys 55	Leu	Ser	Gly	Ser	Gly 60	Ser	Gln	Ser	Asp
Leu 65	Lys	Asp	Val	Ala	Ser	Thr	Ala	Gly	Glü	Glu 75	Gly	Asp	Thr	Ser	Leu 80
	Glu	Ser	Leu	His 85		Val	Thr	Arg	Ser		Lys	Ala	Gly	Cys 95	
Thr	Lys.	Gln	Leu		Ser	Arg	Asn	Cys 105		Glu	Glu	Lys	Ser 110		Gln
Thr	Ser		100 Leu	Lys	Glu	Gly			Asp	Thr	Ser			Phe	Arg
Pro		115 Val	Ser	Pro	Ala	-	120 Gly	Val	Glu	Gly		125 Arg	Val	Asp	Gln
_	130 Asp	Asp	Ģln	Asp		135 Ser	Ser	Leu	Lys		140 Ser	Gln	Asn	Île	
Val	Gln	Thr	Asp		150 Lys	Thr	Ala	: Asp		Glu	Val	Asn	Thr	Asp	160 Gln
Asp	Ile	Glu	Lys	165 Asn	Leu	Asp	Lys		170 Met	Thr	Glu	Arg		175 Leu	Leu
Lys	Glu	Arg	180 Tyr	Gln	Glu	Val	Leu	185 Asp	Lys	Gln	Arg		190 Val	Glu	Asn
Gln	Leu	195 Gln	Val	Gln			200 Gln	Leu	Gln	Gln	Arg	205 Arg	Glu	Ğlu	Glu
Met	210 Lys	Asn	His	Gln		215 Ile	Leu	Lys	Ala		220 Gln	Asp	Val	Thr	
225 Lys	Arg	Glu	Glu		230 Lys	Lys	Lys	Ile	Glu	235 Lys	Glu	Lys	Lys	Glu	240 Phe
Leu	Gln	Lys	Glu	245 Gln	Asp	Leu	Lys	Ala	250 Glu	Ile	Glu	Lys	Leu	255 Cys	Glu
Lys	Gly	Arg	260 Arg	Glu	V al	Tŕp	Glu	265 Met	Glu	Leu	Asp	Arg	270 Leu	Lys	Asn
Gln			Glu			Arg	280 Asn	Ile	Met	Glu	Glu	285 Thr	Glu	Arg	Ala
Trp	290 Lys	Ala	Glu	Ile	Leu	295 Ser	Leu	Glu	Ser	Àrg	300 Lys	Glu	Leu	Leu	Val
305 Leu	Lys	Leu	Glu	Glu	310 Ala	Glu	Lys	Glu	Àla	315 Glu	Leu	His	Leu	Thr	320 Tyr
Leu	Lys.	Ser	Thr	325 Pro	Pro	Thr	Leu	Glu	330 Thr	Val	Arg	Ser	Lys	335 Gln	Glu
•			340 Arg					345					350		٠
		355					360					365		٠.,	Leu
_	370		Pro			375			,		380		٠.		
385			Phe		390	٠,				395					400
		_		405					410					415	
			Pro 420					425			•		430		
		435	Asp	•			440					445	,	4	
Leu	Ser 450	Gln	Pro	Ser	GIn	Pro 455	Ser	Ser	Pro	Leu	Pro 460	GLY	ser	H1S	Gly

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Arg Asn Ser Pro Gly Leu Gly Ser Leu Val Ser
465 470 475
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<210> 194 <211> 241 <212> PRT <213> Homo sapien

<400> 194 Met Ser Gly Glu Ser Ala Arg Ser Leu Gly Lys Gly Ser Ala Pro Pro 1 10 Gly Pro Val Pro Glu Gly Ser Ile Arg Ile Tyr Ser Met Arg Phe Cys 30 25 Pro Phe Ala Glu Arg Thr Arg Leu Val Leu Lys Ala Lys Gly Ile Arg 40 45 His Glu Val Ile Asn Ile Asn Leu Lys Asn Lys Pro Glu Trp Phe Phe Lys Lys Asn Pro Phe Gly Leu Val Pro Val Leu Glu Asn Ser Gln Gly 65 70 75 ... 180 Gln Leu Ile Tyr Glu Ser Ala Ile Thr Cys Glu Tyr Leu Asp Glu Ala - 90 95 Jan 8 1 1284 20 95 Tyr Pro Gly Lys Lys Leu Leu Pro Asp Asp Pro Tyr Glu Lys Ala Cys 105 110 Gln Lys Met Ile Leu Glu Leu Phe Ser Lys Val Pro Ser Leu Val Gly
115 120 125 **125** g g g g g Ser Phe lle Arg Ser Gln Asn Lys Glu Asp Tyr Ala Gly Leu Lys Glu 130 135 140 ar 30 34V Glu Phe Arg Lys Glu Phe Thr Lys Leu Glu Glu Val Leu Thr Asn Lys . 150 155 ... 160 Lys Thr Thr Phe Phe Gly Gly Asn Ser Ile Ser Met Ile Asp Tyr Leu 165 170 Ile Trp Pro Trp Phe Glu Arg Leu Glu Ala Met Lys Leu Asn Glu Cys · 180 - 190 185 Val Asp His Thr Pro Lys Leu Lys Leu Trp Met Ala Ala Met Lys Glu 200 205 Asp Pro Thr Val Ser Ala Leu Leu Thr Ser Glu Lys Asp Trp Gln Gly 215220 Phe Leu Glu Leu Tyr Leu Gln Asn Ser Pro Glu Ala Cys Asp Tyr Gly 230 235 Leu

<210> 195 <211> 138 <212> PRT <213> Homo sapien

<400> 195 🗀

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50
                   55
                                     60
 Gln Gln Glu His Ile His Glu Leu Gln Glu Leu Lys Asp Gln Leu Glu
                70
 Gln Gln Leu Gln Gly Leu His Arg Lys Val Gly Glu Thr Ser Leu Leu
            . 85
                             90
 Leu Ser Gln Arg Glu Gln Glu Ile Val Val Leu Gln Gln Gln Leu Gln
        100
                          105
 Glu Ala Arg Glu Gln Gly Glu Leu Lys Glu Gln Ser Leu Gln Ser Gln
      115
               120
 Leu Asp Glu Ala Gln Arg Ala Leu Ala Gln
    130
                    135
     <210> 196
     <211> 102
      <212> PRT
    <213> Homo sapien
     <400> 196
 Met Ser Lys Arg Lys Ala Pro Gln Glu Thr Leu Asn Gly Gly Ile Thr
 1 5
                             ·10
                                  . 15
 Asp Met Leu Thr Glu Leu Ala Asn Phe Glu Lys Asn Val Ser Gln Ala
   20
                         25
                                 30
 Ile His Lys Tyr Asn Ala Tyr Arg Lys Ala Ala Ser Val Ile Ala Lys
 35
                       40 .
                                      45
 Tyr Pro His Lys Ile Lys Ser Gly Ala Glu Ala Lys Lys Leu Pro Gly 50 60
Val Gly Thr Lys Ile Ala Glu Lys Ile Asp Glu Phe Leu Ala Thr Gly
 65 70
                                75
Lys Leu Arg Lys Leu Glu Lys Ile Arg Gln Asp Asp Thr Ser Ser Ser
 85
                             90
Ile Asn Phe Leu Thr Arg
   100
     <210> 197 -
     <211> 138
     <212> PRT
   <213> Homo sapien
      <400> 197
Glu Ala Asn Glu Val Thr Asp Ser Ala Tyr Met Gly Ser Glu Ser Thr
                10
      5
                                     15
Tyr Ser Glu Cys Glu Thr Phe Thr Asp Glu Asp Thr Ser Thr Leu Val
                             30
                        25
His Pro Glu Leu Gln Pro Glu Gly Asp Ala Asp Ser Ala Gly Gly Ser
35
                     40
                                   45
Ala Val Pro Ser Glu Cys Leu Asp Ala Met Glu Glu Pro Asp His Gly
                  55
                                  60
Ala Leu Leu Leu Pro Gly Arg Pro His Pro His Gly Gln Ser Val
          ··· 70
                               75 80
Ile Thr Val Ile Gly Gly Glu Glu His Phe Glu Asp Tyr Gly Glu Gly
            85
                                 95
                            90
Ser Glu Ala Glu Leu Ser Pro Glu Thr Leu Cys Asn Gly Gln Leu Gly
         100 105
```

Cys Ser Asp Pro Ala Phe Leu Thr Pro Ser Pro Thr Lys Arg Leu Ser

120

115

110

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Ser Lys Lys Val Ala Arg Tyr Leu His Gln
   130
                       135
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<210> 198

<211> 100

<212> PRT

<213> Homo sapien

<400> 198

Met Gly Asp Val Lys Asn Phe Leu Tyr Ala Trp Cys Gly Lys Arg Lys 10 Met Thr Pro Ser Tyr Glu Ile Arg Ala Val Gly Asn Lys Asn Arg Gln 25 -Lys Phe Met Cys Glu Val Gln Val Glu Gly Tyr Asn Tyr Thr Gly Met 35 .. 40 45 Gly Asn Ser Thr Asn Lys Lys Asp Ala Gln Ser Asn Ala Ala Arg Asp 55 . .60. Phe Val Asn Tyr Leu Val Arg Ile Asn Glu Ile Lys Ser Glu Glu Val 75 80 -70 Pro Ala Phe Gly Val Ala Ser Pro Pro Pro Leu Thr Asp Thr Pro Asp 85 90 Thr Thr Ala Asn

100

<210> 199 · ·

∞ <212> PRT :

<213> Homo sapien

<400> 199

Met Val Lys Glu Thr Thr Tyr Tyr Asp Val Leu Gly Val Lys Pro Asn 10 Ala Thr Gln Glu Glu Leu Lys Lys Ala Tyr Arg Lys Leu Ala Leu Lys 2Ŝ 20 Tyr His Pro Asp Lys Asn Pro Asn Glu Gly Glu Lys Phe Lys Gln Ile Ser Gln Ala Tyr Glu Val Leu Ser Asp Ala Lys Lys Arg Glu Leu Tyr 55 Asp Lys Gly Gly Glu Gln Ala Ile Lys Glu Gly Gly Ala Gly Gly Gly 70 75 Phe Gly Ser Pro Met Asp Ile Phe Asp Met Phe Phe Gly Gly Gly 85 90 Arg Met Gln Arg Glu Arg Arg Gly Lys Asn Val Val His Gln Leu Ser 100 105 110 Val Thr Leu Glu Asp Leu Tyr Asn Gly Ala Thr Arg Lys Leu Ala 120 125

<210> 200

<211> 90

<212> PRT

<213> Homo sapien

<400> 200

Met Ala Cys Pro Leu Asp Gln Ala Ile Gly Leu Leu Val Ala Ile Phe 10

<210°> 201 <211> 120 <212> PRT <213> Homo sapien

<400> 201 Met Glu Thr Pro Ser Gln Arg Arg Ala Thr Arg Ser Gly Ala Gln Ala Ser Ser Thr Pro Leu Ser Pro Thr Arg Ile Thr Arg Leu Gln Glu Lys Glu Asp Leu Gln Glu Leu Asn Asp Arg Leu Ala Val Tyr Ile Asp Arg Val Arg Ser Leu Glu Thr Glu Asn Ala Gly Leu Arg Leu Arg Ile Thr 55 Glu Ser Glu Glu Val Val Ser Arg Glu Val Ser Gly Ile Lys Ala Ala 75 70 Tyr Glu Ala Glu Leu Gly Asp Ala Arg Lys Thr Leu Asp Ser Val Ala 90 85 Lys Glu Arg Ala Arg Leu Gln Leu Glu Leu Ser Lys Val Arg Glu Glu 100 105 Phe Lys Glu Leu Lys Ala Arg Asn 115

<210> 202 <211> 177 <212> PRT <213> Homo sapien

 <400>
 202

 Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Ile
 1

 1
 5
 10

 Lys Met Glu Glu Glu Ser Gly Ala Pro Gly Val Pro Ser Gly Asn Gly
 20

 20
 25
 30

 Ala Pro Gly Pro Lys Gly Glu Gly Glu Arg Pro Ala Gln Asn Glu Lys
 45

 Arg Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr
 50
 60

 Ala Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe
 75
 80

 Asp Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly
 85
 90
 95

 Glu Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg
 100
 105
 110

 Gly Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala

<210> 203 <211> 164 <212> PRT <213> Homo sapien

<400> 203

Met Arg Leu Ala Val Gly Ala Leu Leu Val Cys Ala Val Leu Gly Leu 5 -- 10 15 Cys Leu Ala Val Pro Asp Lys Thr Val Arg Trp Cys Ala Val Ser Glu 20 . 25 His Glu Ala Thr Lys Cys Gln Ser Phe Arg Asp His Met Lys Ser Val 40 IIe Pro Ser Asp Gly Pro Ser Val Ala Cys Val Lys Lys Ala Ser Tyr 60 ... Leu Asp Cys Ile Arg Ala Ile Ala Ala Asn Glu Ala Asp Ala Val Thr 70 75 Leu Asp Ala Gly Leu Val Tyr Asp Ala Tyr Leu Ala Pro Asn Asn Leu 90 Lys Pro Val Val Ala Glu Phe Tyr Gly Ser Lys Glu Asp Pro Gln Thr 100 105 Phe Tyr Tyr Ala Val Ala Val Val Lys Lys Asp Ser Gly Phe Gln Met 115 120 Asn Gln Leu Arg Gly Lys Lys Ser Cys His Thr Gly Leu Gly Arg Ser 135 140 Ala Gly Trp Asn Ile Pro Ile Gly Leu Leu Tyr Cys Asp Leu Pro Glu 155 Pro Arg Lys Pro

<210> 204 <211> 241 <212> PRT <213> Homo sapien

<400> 204

 Met
 Ser
 Gly
 Glu
 Ser
 Ala
 Arg
 Ser
 Leu
 Gly
 Lys
 Gly
 Ser
 Ala
 Pro
 Pro
 Pro
 Pro
 Glu
 Gly
 Ser
 Ile
 Arg
 Ile
 Tyr
 Ser
 Met
 Arg
 Phe
 Cys

 20
 20
 25
 30
 30
 30
 30
 30
 40
 Arg
 Ala
 Lys
 Gly
 Ile
 Arg
 Arg
 Arg
 Leu
 Val
 Leu
 Lys
 Ala
 Lys
 Gly
 Ile
 Arg
 <

Gln Leu Ile Tyr Glu Ser Ala Ile Thr Cys Glu Tyr Leu Asp Glu Ala 85 90 Tyr Pro Gly Lys Lys Leu Leu Pro Asp Asp Pro Tyr Glu Lys Ala Cys 100 105 Gln Lys Met Ile Leu Glu Leu Phe Ser Lys Val Pro Ser Leu Val Gly 125 115 120 Ser Phe Ile Arg Ser Gln Asn Lys Glu Asp Tyr Asp Gly Leu Lys Glu 130 135 140 Glu Phe Arg Lys Glu Phe Thr Lys Leu Glu Glu Val Leu Thr Asn Lys 155 150 Lys Thr Thr Phe Phe Gly Gly Asn Ser Ile Ser Met Ile Asp Tyr Leu 170 175 165 Ile Trp Pro Trp Phe Glu Arg Leu Glu Ala Met Lys Leu Asn Glu Cys 185 Val Asp His Thr Pro Lys Leu Lys Leu Trp Met Ala Ala Met Lys Glu 200 Asp Pro Thr Val Ser Ala Leu Leu Thr Ser Glu Lys Asp Trp Gln Gly Phe Leu Glu Leu Tyr Leu Gln Asn Ser Pro Glu Ala Cys Asp Tyr Gly **225** 230 235 Leu

<210> 205 <211> 160 <212> PRT <213> Homo sapien

<400> 205

Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu 1 5 10 Val Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp 25 Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys 35 40 Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu 50 55 Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe 65 70 75 Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Pro Ser 90 85 Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile 100 105 Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp 120 Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His 130 : 135 140 Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys Thr Leu 145 150 155 160

<210> 206

<211> 197

<212> PRT

<213> Homo sapien

<400> 206 Thr Ser Pro Ser Glu Ala Cys Ala Pro Leu Leu Ile Ser Leu Ser Thr 5 10 Leu Ile Tyr Asn Gly Ala Leu Pro Cys Gln Cys Asn Pro Gln Gly Ser 20 25 Leu Ser Ser Glu Cys Asn Pro His Gly Gly Gln Cys Leu Cys Lys Pro 40 Gly Val Val Gly Arg Arg Cys Asp Leu Cys Ala Pro Gly Tyr Tyr Gly Phe Gly Pro Thr Gly Cys Gln Gly Ala Cys Leu Gly Cys Arg Asp His Thr Gly Gly Glu His Cys Glu Arg Cys Ile Ala Gly Phe His Gly Asp Pro Arg Leu Pro Tyr Gly Gly Gln Cys Arg Pro Cys Pro Cys Pro Glu 100 105 Gly Pro Gly Ser Gln Arg His Phe Ala Thr Ser Cys His Gln Asp Glu 115 120 125 Tyr Ser Gln Gln Ile Val Cys His Cys Arg Ala Gly Tyr Thr Gly Leu 135 Arg Cys Glu Ala Cys Ala Pro Gly His Phe Gly Asp Pro Ser Arg Pro 150 155 Gly Gly Arg Cys Gln Leu Cys Glu Cys Ser Gly Asn Ile Asp Pro Met 170 165 Asp Pro Asp Ala Cys Asp Pro His Thr Gly Gln Cys Leu Arg Cys Leu His His Thr Glu Gly

<210> 207 <211> 175 <212> PRT <213> Homo sapien

<400> 207 Ile Ile Arg Gln Gln Gly Leu Ala Ser Tyr Asp Tyr Val Arg Arg Arg 10 Leu Thr Ala Glu Asp Leu Phe Glu Ala Arg Ile Ile Ser Leu Glu Thr Tyr Asn Leu Leu Arg Glu Gly Thr Arg Ser Leu Arg Glu Ala Leu Glu 40 Ala Glu Ser Ala Trp Cys Tyr Leu Tyr Gly Thr Gly Ser Val Ala Gly 55 Val Tyr Leu Pro Gly Ser Arg Gln Thr Leu Ser Ile Tyr Gln Ala Leu 70 75 Lys Lys Gly Leu Leu Ser Ala Glu Val Ala Arg Leu Leu Glu Ala 90 Gln Ala Ala Thr Gly Phe Leu Leu Asp Pro Val Lys Gly Glu Arg Leu 105 Thr Val Asp Glu Ala Val Arg Lys Gly Leu Val Gly Pro Glu Leu His 120 Asp Arg Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Arg Asp Pro . 135 140 Tyr Thr Glu Gln Thr Ile Ser Leu Phe Gln Ala Met Lys Lys Glu Leu 150 155 Ile Pro Thr Glu Glu Ala Leu Arg Leu Trp Met Pro Ser Trp Pro

165 170 175

<210> 208 <211> 177 <212> PRT <213> Homo sapien

<400> 208

Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Ile 10 Lys Met Glu Glu Glu Ser Gly Ala Pro Gly Val Pro Ser Gly Asn Gly 20 25 Ala Pro Gly Pro Lys Gly Glu Gly Glu Arg Pro Ala Gln Asn Glu Lys a∈ 40 Arg Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr 55 60 Ala Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe 65 70 75 80 Asp Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly 85 tvi -90. Glu Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg 100 ··· 105 -Gly Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala 115 120 125 Ala Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val 135 140 Lys Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Val 150 155 Met Ala Thr Thr Gly Gly Met Gly Met Gly Pro Gly Pro Gly Met 170 175 Ile

<210> 209 <211> 196 <212> PRT <213> Homo sapien

2004 CON 573 1 188 L 8 <400> 209 - €.1 Asp Leu Gln Asp Met Phe Ile Val His Thr Ile Glu Glu Ile Glu Gly 10 Leu Ile Ser Ala His Asp Gln Phe Lys Ser Thr Leu Pro Asp Ala Asp 20 25 Arg Glu Arg Glu Ala Ile Leu Ala Ile His Lys Glu Ala Gln Arg Ile 35 40 Ala Glu Ser Asn His Ile Lys Leu Ser Gly Ser Asn Pro Tyr Thr Thr 55 60 te Val Thr Pro Gln Ile Ile Asn Ser Lys Trp Glu Lys Val Gln Gln Leu 70 75 Val Pro Lys Arg Asp His Ala Leu Leu Glu Glu Gln Ser Lys Gln Gln 90 Ser Asn Glu His Leu Arg Arg Gln Phe Ala Ser Gln Ala Asn Val Val 105 Gly Pro Trp Ile Gln Thr Lys Met Glu Glu Ile Gly Arg Ile Ser Ile 115 125

```
Glu Met Asn Gly Thr Leu Glu Asp Gln Leu Ser His Leu Lys Gln Tyr
                    135
                                      140
 Glu Arg Ser Ile Val Asp Tyr Lys Pro Asn Leu Asp Leu Leu Glu Gln
                                   155 ..
Gln His Gln Leu Ile Gln Glu Ala Leu Ile Phe Asp Asn Lys His Thr
  165
                               170
 Asn Tyr Thr Met Glu His Ile Arg Val Gly Trp Glu Gln Leu Leu Thr
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Thr Ile Ala Arg
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      <210> 210
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Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly Lys Glu
1 5 10 15
Val Leu Leu Leu Ala His Asn Leu Pro Gln Asn Arg Ile Gly Tyr Ser
 20 25
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Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Ser Leu Ile Val Gly Tyr
 35 40
Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Tyr Ser Gly Arg
50 55 60
Glu Thr Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Val Thr Gln
                 70
Asn Asp Thr Gly Phe Tyr Thr Leu Gln Val Ile Lys Ser Asp Leu Val
              85
                                90
Asn Glu Glu Ala Thr Gly Gln Phe His Val Tyr Pro Glu Leu Pro Lys
          100
                           105
                                             110
Pro Ser Ile Ser Ser Asn Asn Ser Asn Pro Val Glu Asp Lys Asp Ala
    115
                       120
Val Ala Phe Thr Cys Glu Pro Glu Val Gln Asn Thr Thr Tyr Leu Trp
                                      140
                    135
Trp Val Asn Gly Gln Ser Leu Pro Val Ser Pro Lys
       .. £
                 150
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     <211> 92
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Met Glu Ser Pro Ser Ala Pro Pro His Arg Trp Cys Ile Pro Trp Gln
5 7 10
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Arg Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr
  20 25 30
Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly
   35 40
                                         45
Lys Glu Val Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly
                     55
                                      60
Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Ile
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Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly

85

90

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Glu Lys Gln Lys Asn Lys Glu Phe Ser Gln Thr Leu Glu Asn Glu Lys 10 Asn Thr Leu Leu Ser Gln Ile Ser Thr Lys Asp Gly Glu Leu Lys Met 20 25 30 Leu Gln Glu Glu Val Thr Lys Met Asn Leu Leu Asn Gln Gln Ile Gln 40 Glu Glu Leu Ser Arg Val Thr Lys Leu Lys Glu Thr Ala Glu Glu Glu 55 60 Lys Asp Asp Leu Glu Glu Arg Leu Met Asn Gln Leu Ala Glu Leu Asn 70 Gly Ser Ile Gly Asn Tyr Cys Gln Asp Val Thr Asp Ala Gln Ile Lys 85 90 95 Asn Glu Leu Leu Glu Ser Glu Met Lys Asn Leu Lys Lys Cys Val Ser 100 105 Glu Leu Glu Glu Glu Lys Gln Gln Leu Val Lys Glu Lys Thr Lys Val 120 Glu Ser Glu Ile Arg Lys Glu Tyr Leu Glu Lys Ile Gln Gly 135 .. 140

<210> 213
<211> 142
<212> PRT
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Gly Gly Tyr Gly Gly Gly Tyr Gly Gly Val Leu Thr Ala Ser Asp Gly 1 10 Leu Leu Ala Gly Asn Glu Lys Leu Thr Met Gln Asn Leu Asn Asp Arg 20 Leu Ala Ser Tyr Leu Asp Lys Val Arg Ala Leu Glu Ala Ala Asn Gly 40 45 Glu Leu Glu Val Lys Ile Arg Asp Trp Tyr Gln Lys Gln Gly Pro Gly 55 60 Pro Ser Arg Asp Tyr Ser His Tyr Tyr Thr Thr Ile Gln Asp Leu Arg 70 75 Asp Lys Ile Leu Gly Ala Thr Ile Glu Asn Ser Arg Ile Val Leu Gln 90 25 95 - : 85 Ile Asp Asn Ala Arg Leu Ala Ala Asp Asp Phe Arg Thr Lys Phe Glu 100 Thr Glu Gln Ala Leu Arg Met Ser Val Glu Ala Asp Ile Asn Gly Leu 115 120 125 Arg Arg Val Leu Asp Glu Leu Thr Leu Ala Arg Thr Asp Leu 135 130

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<213> Homo sapien

<400>. 214 Val Met Arg Val Asp Phe Asn Val Pro Met Lys Asn Asn Gln Ile Thr 15 miles 10 miles 15 Asn Asn Gln Arg Ile Lys Ala Ala Val Pro Ser Ile Lys Phe Cys Leu 20 25 30 Asp Asn Gly Ala Lys Ser Val Val Leu Met Ser His Leu Gly Arg Pro (1) 35 (1) (1) (1) (1) (1) (40 (1) (1) (1) (1) (1) (45 (1) (1) (1) (1) Asp Gly Val Pro Met Pro Asp Lys Tyr Ser Leu Glu Pro Val Ala Val - A - 1 - 1942、1**55**g - 195g - 195g - 1**60**元かま かぶる かかむ Glu Leu Arg Ser Leu Leu Gly Lys Asp Val Leu Phe Leu Lys Asp Cys Val Gly Pro Glu Val Glu Lys Ala Cys Ala Asn Pro Ala Ala Gly Ser Val Ile Leu Leu Glu Asn Leu Arg Phe His Val Glu Glu Gly Lys 100. Gly Lys Asp Ala Ser Gly Asn Lys Val Lys Ala Glu Pro Ala Lys Ile 115

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Leu Ala Leu Val Asp Val Leu Glu Asp Lys Leu Lys Gly Glu Met Met

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55
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70
75
80
Asp Lys Asp Tyr Ser Val Thr Ala Asn Ser Lys Ile Val Val Val Thr

Asp Lys Asp Tyr Ser Val Thr Ala Asn Ser Lys Ile Val Val Val Thr
85 90 95
Ala Gly Val Arg Gln Gln Glu Gly Glu Ser Arg Leu Asn Leu Val Gln

Arg Asn Val Asn Val Phe Lys Phe Ile Ile Pro Gln Ile Val Lys Tyr 115 120 125

Ser Pro Asp Cys Ile Ile Ile Val Val Ser Asn Pro Val Asp Ile Leu

130

135

140

Thr Tyr Val Thr

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<211> 527

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 $(v_1, v_2, \dots, v_n) \in \mathcal{F}(G_n) \times \mathbb{R}^n$

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	Pro	Gly	Asp	Gly	Phe	Pro	Ser	Asn	Asp	Ser	Gly	Phe	Gly	Gly	Ser	Phe
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		Trp		Glu	Asp	Phe	Pro	Leu	Leu	Pro	Pro	Pro	Gly	Pro	Pro	Leu
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	Cys	Phe	Ser	Arg	Phe	Ser	Val	Ser	Pro	Ala	Leu	Glu	Thr	Pro	Gly	Pro
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WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/12, A61K 38/17, C07K 14/47, 16/18, A61K 35/14	A3	(11) International Publication Number: WO 99/38973 (43) International Publication Date: 5 August 1999 (05.08.99)
(21) International Application Number: PCT/US9 (22) International Filing Date: 26 January 1999 (2 (30) Priority Data: 09/015,029 28 January 1998 (28.01.98) 09/015,022 28 January 1998 (28.01.98) 09/040,828 18 March 1998 (18.03.98) 09/040,831 18 March 1998 (18.03.98) 09/122,192 23 July 1998 (23.07.98) 09/122,191 23 July 1998 (23.07.98) 09/122,191 23 July 1998 (23.07.98) 09/219,245 22 December 1998 (22.12.98) (71) Applicant: CORIXA CORPORATION [US/US]; Sull 1124 Columbia Street, Seattle, WA 98104 (US). (72) Inventors: REED, Steven, G.; 2843 – 122nd Pla Bellevue, WA 98005 (US). LODES, Michael, J.; 36th Avenue S.W., Seattle, WA 98126 (US). FRU Tony, N.; P.O. Box 99232, Seattle, WA 99232-02 MOHAMATH, Raodoh; 4205 South Morgan, Seat 98118 (US). (74) Agents: MAKI, David, J. et al.; Seed and Ber 6300 Columbia Center, 701 Fifth Avenue, Seat 98104-7092 (US).	26.01.9 [BY, CA, CH, CN, CU, CZ, DB, DK, EB, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TI, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Burasian patent (AM, AZ, BY, KG, KZ, MD, RU, TI, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NIL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claim and to be republished in the event of the receipt of amendments. (88) Date of publication of the international search report: 9 December 1999 (09.12.99

(57) Abstract

Compounds and methods for treating lung cancer are provided. The inventive compounds include polypeptides containing at least a portion of a lung tumor protein. Vaccines and pharmaceutical compositions for immunotherapy of lung cancer comprising such polypeptides, or polynucleotides encoding such polypeptides, are also provided, together with polymeleotides for preparing the inventive polypeptides.

INTERNATIONAL SEARCH REPORT

Inte in sonal Application No PCT/US 99/01642

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A CLASSIF IPC 6	C12N15/12 A61K38/17 C07K14	/47 C07K16/18	A61K35/14
According to	International Patent Classification (IPC) or to both national classific	ication and IPC	
3. FIELDS	SEARCHED		
	currentation searched (classification system followed by classification C12N C12Q A61K C97K	ation symbols)	
Documentati	ion searched other than minimum documentation to the extent that	t such documents are included in the	fields searched
lectronio de	ata base consulted during the international search (name of data t	sese and, where practical, search ter	ms used)
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C. DOCUME	ENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the	relevant passages	Relevant to claim No.
A	WO 96 30389 A (MILLENIUM PHARMA INC.; SHYJAN A.) 3 October 1996 see page 112 - page 127		1-60
A	WO 96 02552 A (CYTOCLONYL PHARM INC.; TORCZYNSKI R. ET AL.) 1 F 1996 see the whole document	ACEUTICS, ebruary	1-60
A	YOU L ET AL.: "Identification growth response gene-1 (Egr-1) phorbol myristate-induced gene cancer cells by differential mF AM. J. RESPIR. CELL MOL. BIOL., vol. 17, no. 5, November 1997, pages 617-624, XP002106654	as a in lung RNA display"	1,2,4-7
हर	see page 618, left-hand column,	, paragraph	
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X Furt	her documents are listed in the continuation of box C.	X Palent family members	are listed in annex.
"A" docum consider "E" earfer filing ("L" docum which citatio "O" docum other "P" docum	stagories of cited documents: ent defining the general state of the art which is not dered to be of particular relevance document but published on or after the international date ent which may throw doubts on priority claim(s) or is oited to establish the publication date of another in or other special reason (as specified) sent referring to an oral disclosure, use, exhibition or means ent published prior to the international filing date but than the priority date claimed	cited to understand the prin invention "X" document of perfouter releve connot be considered nove involve an inventive step wi "Y" document of perfouter releve cannot be considered to in- document to combined with	ordict with the application but oiple or theory underlying the arros; the claimed invention I or cannot be considered to hen the document is taken alone arros; the claimed invention rolve an inventive step when the one or more other such docu- eing obvious to a person skilled
	actual completion of the international search	Date of mailing of the intern	ational search report
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	European Patent Office, P.B. 5818 Patentinan 2 NL - 2280 HV Rijesrijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	CUPIDO, M	

INTERNATIONAL SEARCH REPORT

s International Search Report h	has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:	
X Claims Nos.:	and the second s	
•	ubject matter not required to be searched by this Authority, namely: gh_claims_16,_17,_24-26,_32,_33,_48-53_and_56-58_are	
remark: Althoug	ed to a method of treatment of the human/animal body	
	arch has been carried out and based on the alleged	
effects	s of the composition.	
Claims Nos.:		
because they relate to pa	arts of the International Application that do not comply with the prescribed requirements to such agful International Search can be carried out, specifically:	
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Claims Nos.: because they are depend	ident claims and are not draited in accordance with the second and third sentences of Rule 6.4(a).	
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	s could be searched without effort justifying an additional fee, this Authority did not invite payment	-
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INTERNATIONAL SEARCH REPORT

Information on patent family members ...

Inte onal Application No PCT/US 99/01642

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